REASANZ™ (Serelaxin)
BLA 125,468

Cardiovascular and Renal Drugs Advisory Committee Meeting

March 27, 2014

Novartis Pharmaceuticals Corporation

Introduction

Ameet Nathwani, MD

Global Head, Critical Care
Novartis Pharma AG

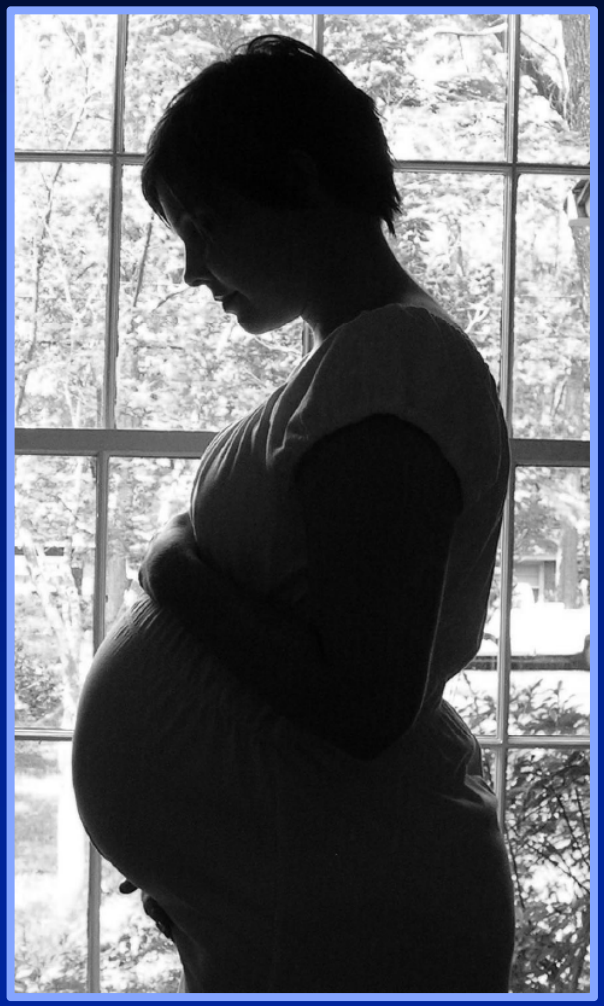
Acute Heart Failure – Life Threatening Condition With a Prognosis Worse Than Many Cancers[2,3]

- AHF is the most frequent cause of hospitalization in patients aged >65 years[1]
  - 10-12% mortality after 30 days
  - 20-35% mortality at 1 year
- Main treatment goals are to feel better and live longer through
  - Improvement in current clinical status
  - Prevention of worsening clinical status
  - Reduction in risk of death
- Therapeutic approach to AHF has not changed significantly in the last three decades[4]

1. Hunt et al. J Am Coll Cardiol 2009;53:e1–90; 2. Gheorghiade & Pang. J Am Coll Cardiol 2009;53:557–73;
3. Askoxylakis et al. BMC Cancer 2010;10:105; 4. Felker et al. Circ Heart Fail 2010;3:314–25

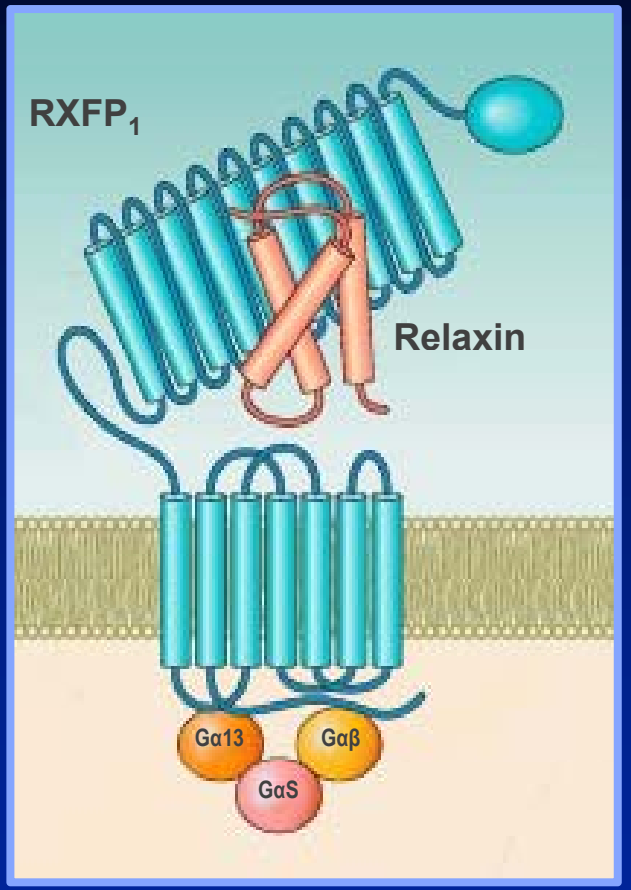
Serelaxin – a Recombinant Form of the Endogenous Human Peptide Hormone Relaxin

- Relaxin levels are elevated during pregnancy when adaptive systemic hemodynamic and renal changes occur



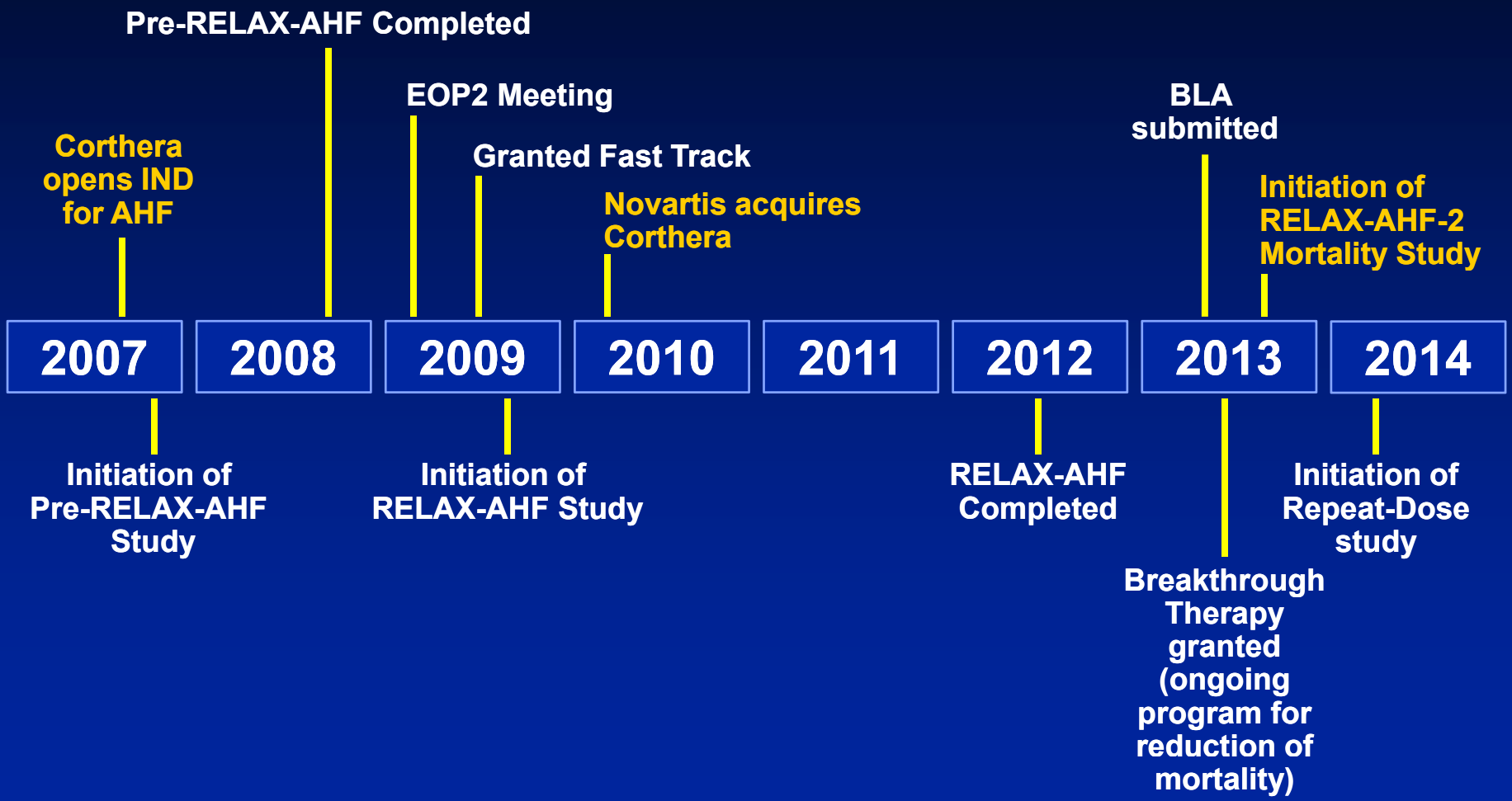
Relaxin – a Hormonal Mediator With Multiple Actions

- Relaxin acts by binding to its cognate G protein-coupled receptor – relaxin family peptide (RXFP1) located in:
  - Systemic, coronary and renal vasculature
  - Cardiac tissue and renal epithelium
- Relaxin primarily stimulates both the rapid and sustained nitric oxide (NO) – mediated vasodilation pathways



Teichman et al. Heart Fail Rev 2009;14:321–9; Jeyabalan et al. Adv Exp Med Biol 2007;612:65–87; Kong et al. Moll Cell Endocrinol 2010;320:1–15; Du et al. Nat Rev Cardiol 2010;7:48–58; Novak J. et al. FASEB J. 2006; 20: 2352–2362, Hsu et al 2002, Dschietzig et al 2011

Serelaxin Program in Acute Heart Failure



Key Clinical Studies in Acute Heart Failure

	Study	Objective	Study Size*
Efficacy and Safety	Pre-RELAX-AHF	Dose Ranging and Efficacy and Safety	234
	RELAX-AHF	Efficacy and Safety	1161
Mechanistic	A2201	Central Hemodynamics	71

* Number of patients randomized

Serelaxin Proposed Indication and Dosing

- Indication
  - To improve the symptoms of acute heart failure through reduction of the rate of worsening heart failure
- Dosing Regimen
  - Weight based dosing over 48 hours delivering ~ 30 µg/kg/day
  - Infusion initiated as soon as possible after hospital admission

Presentation Overview

Introduction	***Ameet Nathwani, MD*** Global Head, Critical Care Novartis Pharma AG
Challenges in Drug Development in Acute Heart Failure	***Milton Packer, MD*** Professor and Chair of Department of Clinical Sciences, UT Southwestern Medical Center
RELAX-AHF Trial Design and Primary Endpoint Results	***Olga Santiago, MD*** Executive Global Program Head, Critical Care Novartis Pharmaceuticals Corporation
Additional Efficacy and Safety Results	***Thomas Severin, MD*** Global Program Medical Director, Critical Care Novartis Pharma AG
Final Commentary and Clinical Perspective	***Milton Packer, MD*** Professor and Chair of Department of Clinical Sciences, UT Southwestern Medical Center

Experts Available for Questions

- **Barry H. Greenberg, MD, FACC**
  Professor of Medicine, Director, Advanced Heart Failure Treatment Program, University of California San Diego
- **Beth Davison, PhD**
  Vice President, Biometrics, Momentum Research Inc.
- **Gad Cotter, MD, FACC, FESC**
  President and CEO, Momentum Research, Inc.
- **Chad Gwaltney, PhD**
  Senior Director, eRT, Inc.
- **Gary Koch, PhD**
  Professor of Biostatistics, University of North Carolina at Chapel Hill

How Can We Evaluate Clinical Benefits in Trials of New Drugs for Acute Heart Failure?

Milton Packer, M.D.
University of Texas Southwestern Medical Center
Dallas, Texas

Evaluating the Effects of New Drugs for Acute and Chronic Heart Failure

- Improvement in current clinical status
- Prevention of worsening clinical status
- Reduction in the risk of death

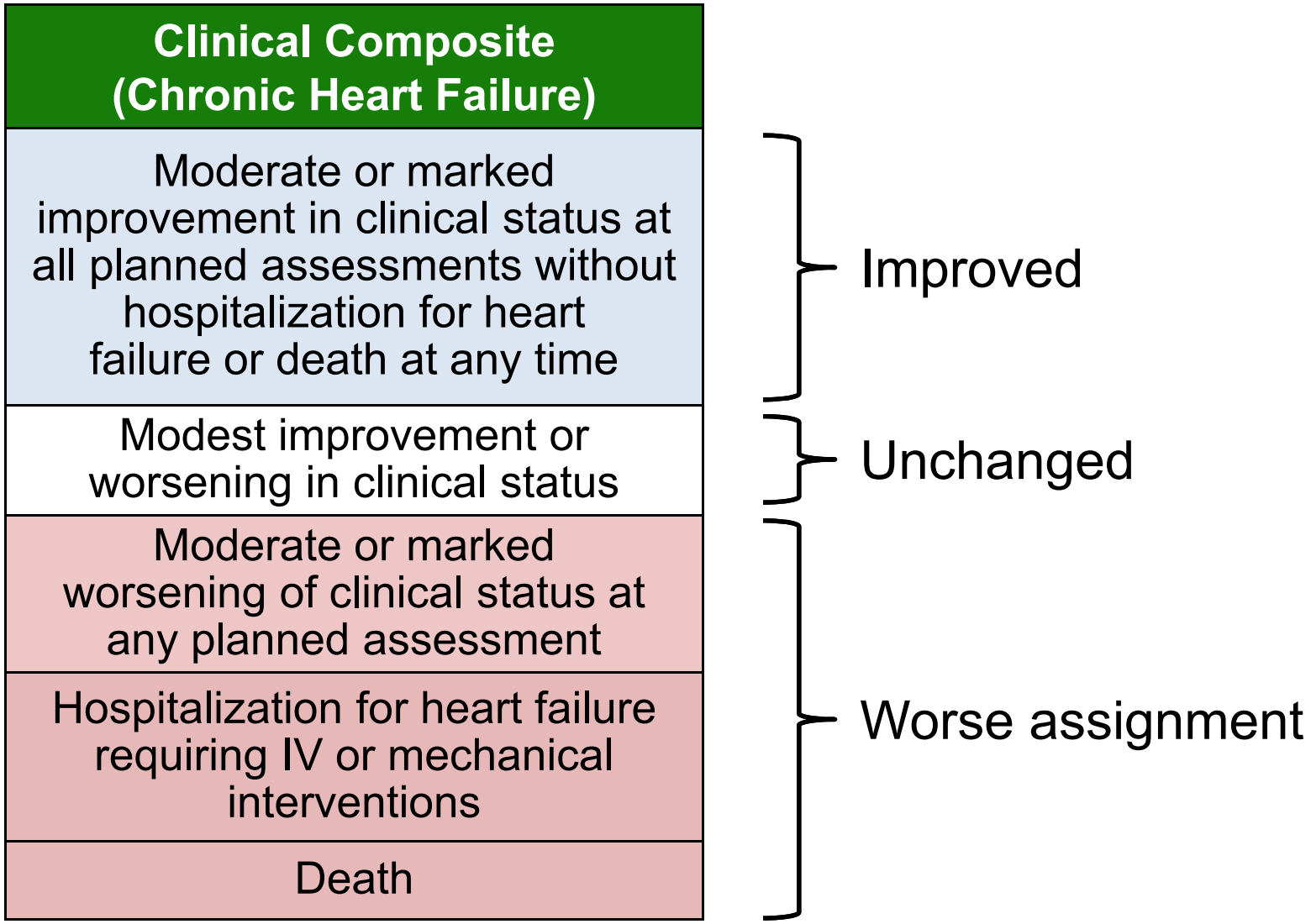
How Can We Evaluate Clinical Benefits in Trials of New Drugs for Heart Failure?

	Chronic Heart Failure	Acute Heart Failure
Improvement of current clinical status	NYHA class Dyspnea scores Global assessment 6-min walk VO_2max Quality of life	
Prevention of worsening clinical status		
Reduction in risk of death		

How Can We Evaluate Clinical Benefits in Trials of New Drugs for Heart Failure?

	Chronic Heart Failure	Acute Heart Failure
Improvement of current clinical status	NYHA class Dyspnea scores Global assessment 6-min walk VO_2max Quali of life	
Prevention of worsening clinical status	Hospitalization for heart failure	
Reduction in risk of death	All-cause or cardiovascular mortality	

Clinical Composite: Incorporating Morbidity Into a Symptom Assessment



How Can We Evaluate Clinical Benefits in Trials of New Drugs for Heart Failure?

	Chronic Heart Failure	Acute Heart Failure
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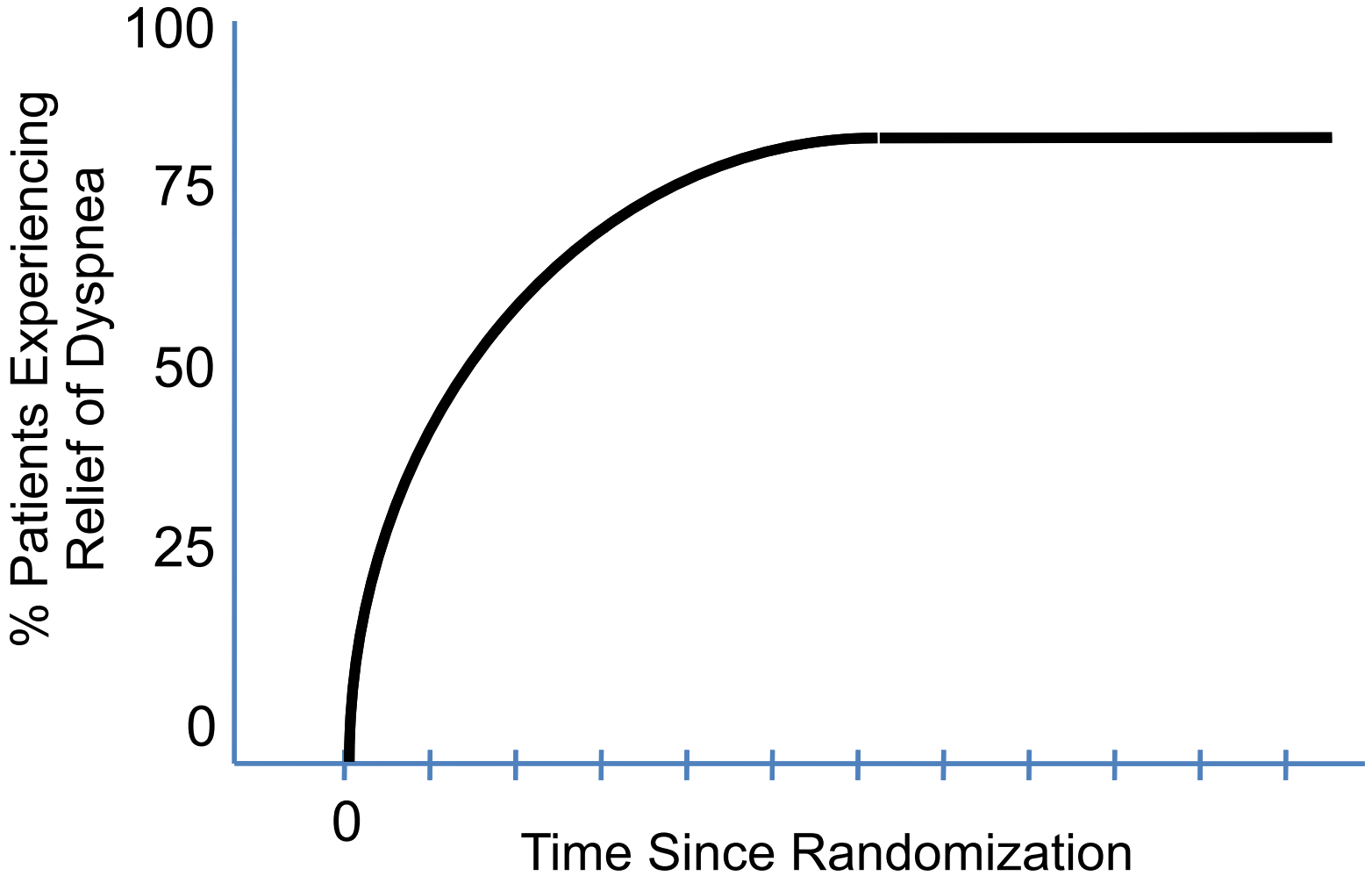
Prevention of worsening clinical status	Hospitalization for heart failure	
Reduction in risk of death	All-cause or cardiovascular mortality	

Time Course of Dyspnea Relief With Current Treatment in Acute Heart Failure



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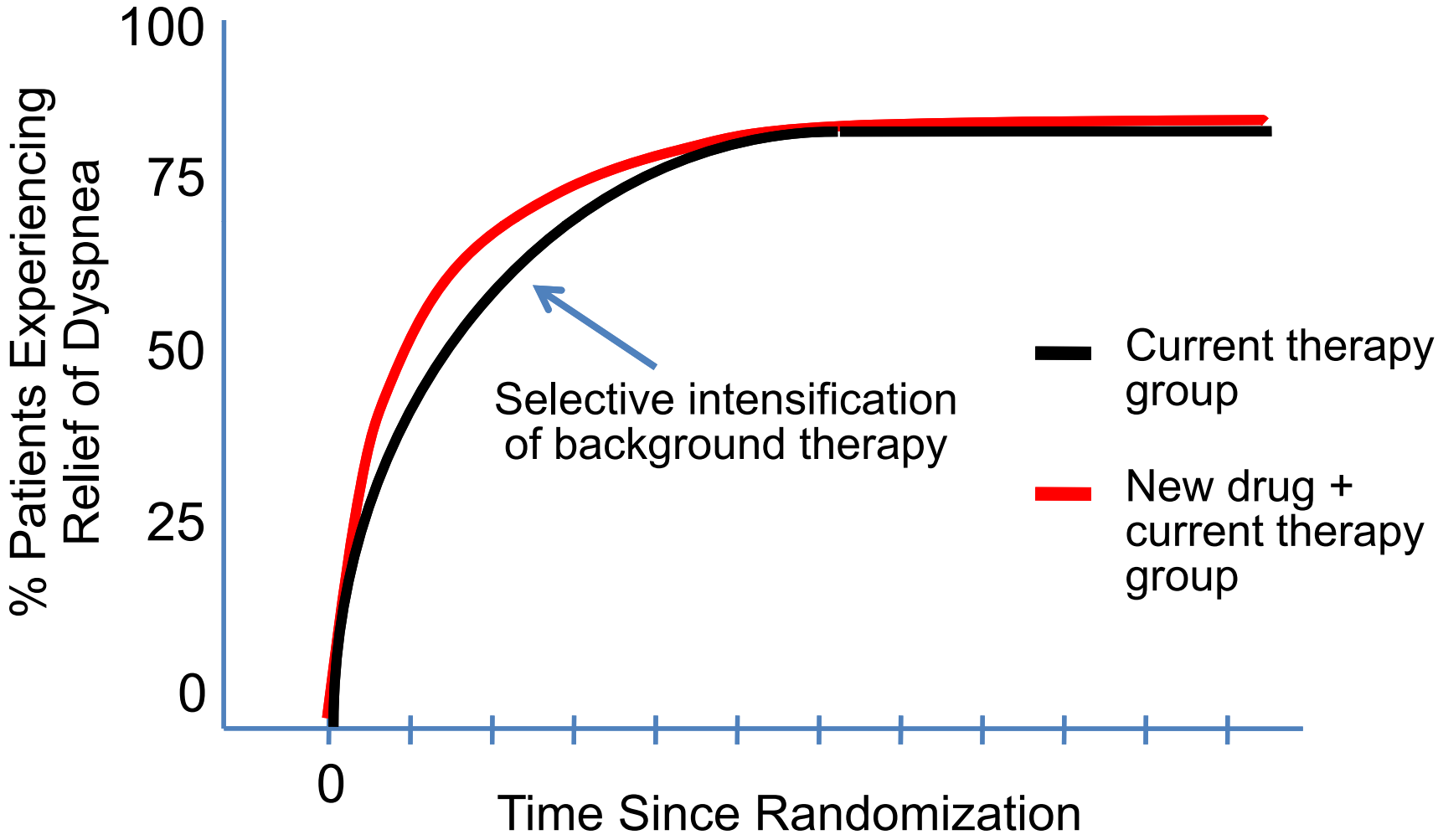
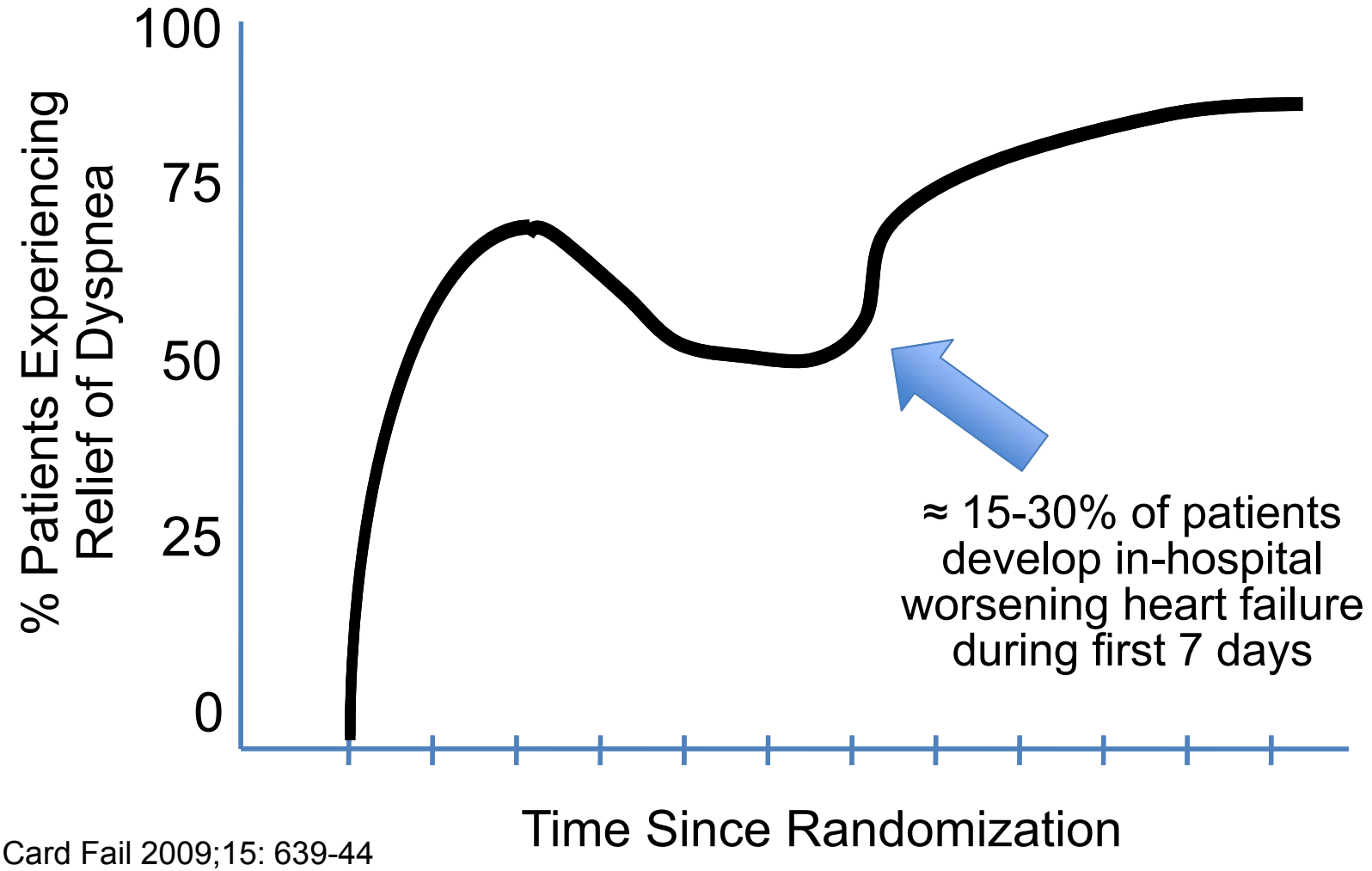


How Can We Evaluate Clinical Benefits in Trials of New Drugs for Heart Failure?

	Chronic Heart Failure	Acute Heart Failure
Improvement of current clinical status	NYHA class Dyspnea scores Global assessment 6-min walk VO_2max Quali of life	Dyspnea scores Global assessment
Prevention of worsening clinical status	Hospitalization for heart failure	In-hospital worsening heart failure
Reduction in risk of death	All-cause or cardiovascular mortality	All-cause or cardiovascular mortality

In-Hospital Worsening Heart Failure Is an Important Event in Acute Heart Failure



J Card Fail 2009;15: 639-44
Fundam Clin Pharmacol 2009;23:633-9

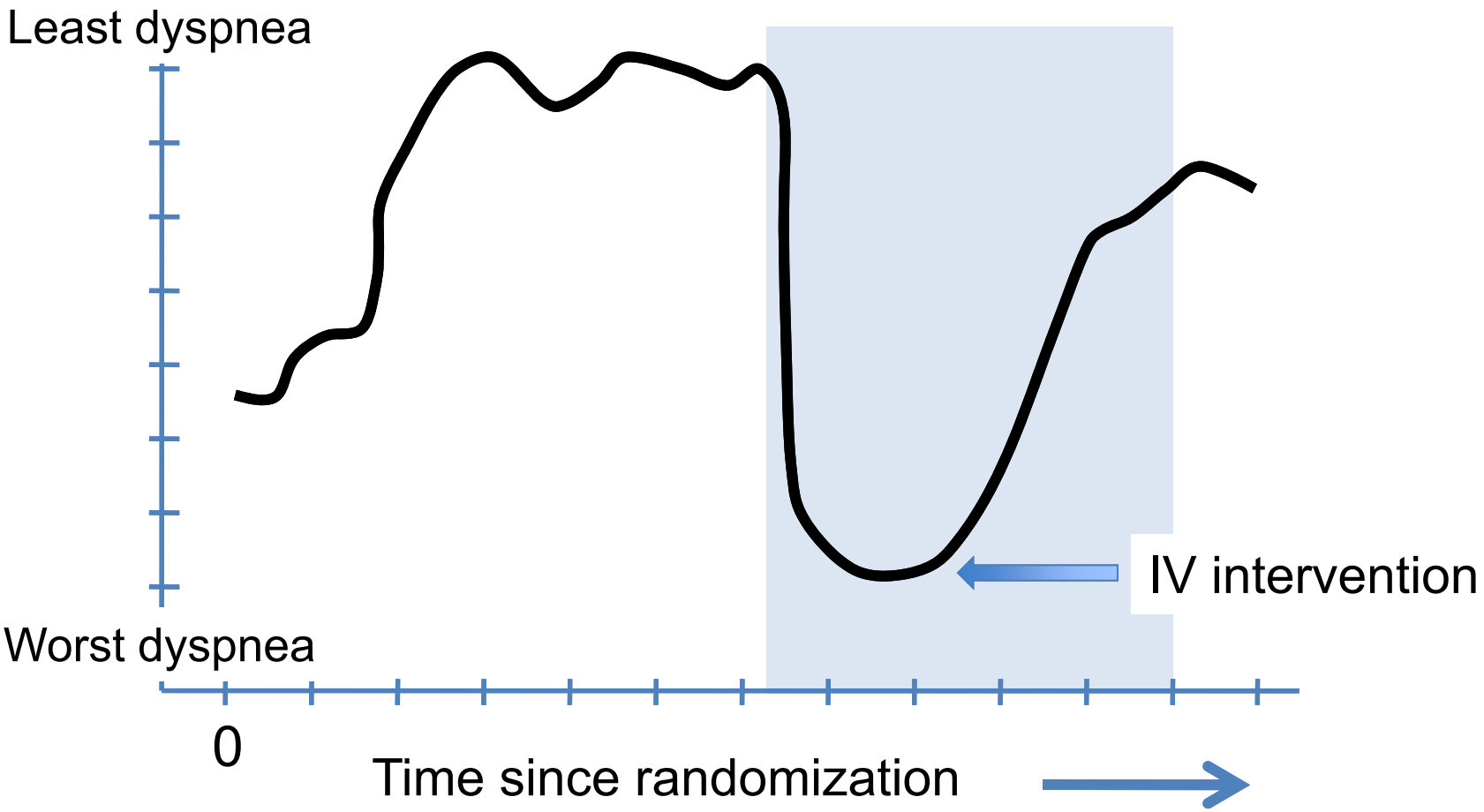
Identification of In-Hospital Worsening Heart Failure Events in Clinical Trials

	Evidence for Clinical Deterioration	Criteria for Identification of Event
Chronic heart failure	Hospitalization for heart failure	Worsening of clinical status Intensification of therapy for heart failure
Acute heart failure	In-hospital worsening heart failure	

Why Do We Need to Focus on In-Hospital Worsening Heart Failure?

- Represents a meaningfully unfavorable change in clinical status, signifying instability in the patient's clinical course.

In-Hospital Worsening Heart Failure Represents Failure of Prescribed Therapy to Maintain Clinical Stability

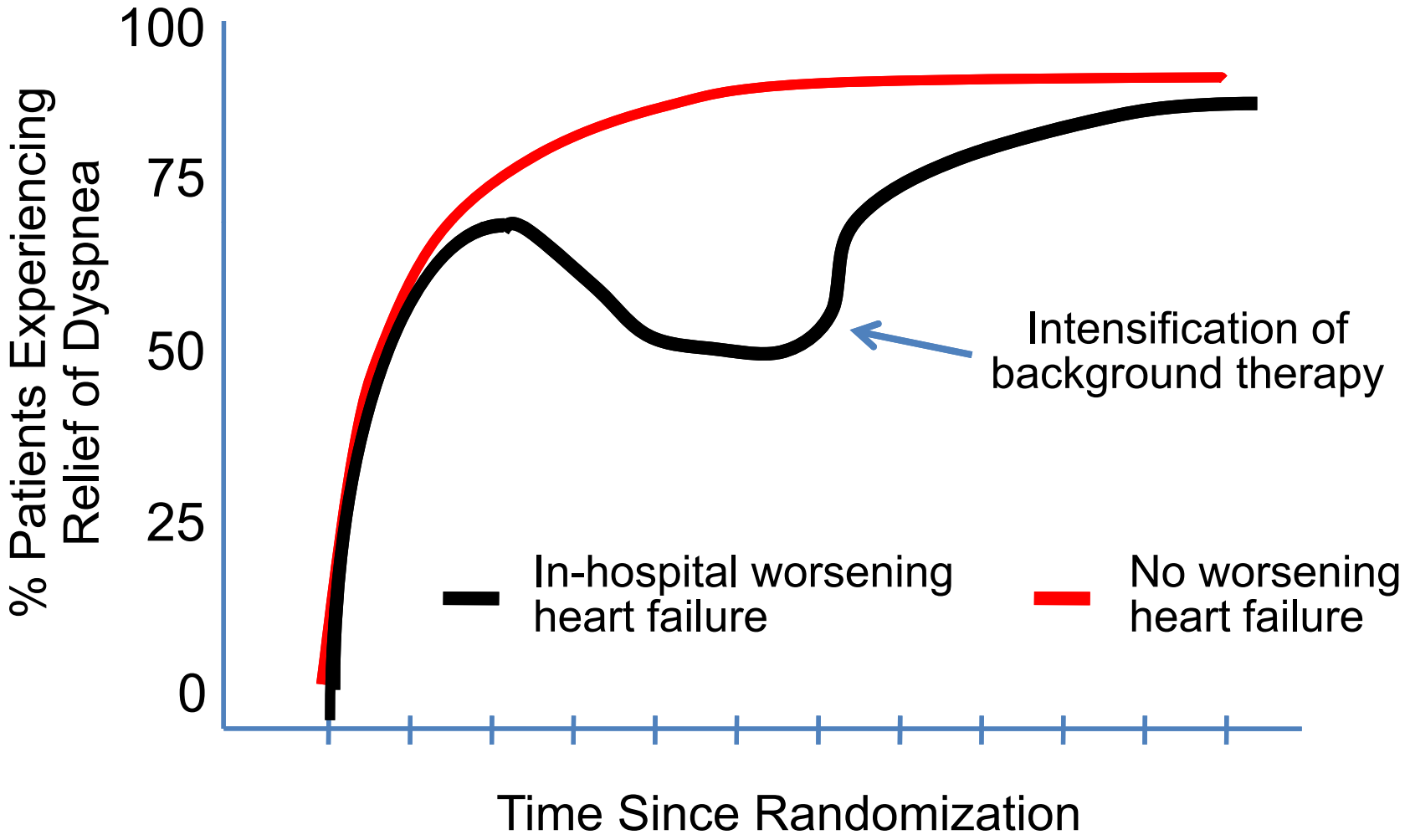


Why Do We Need to Focus on In-Hospital Worsening Heart Failure?

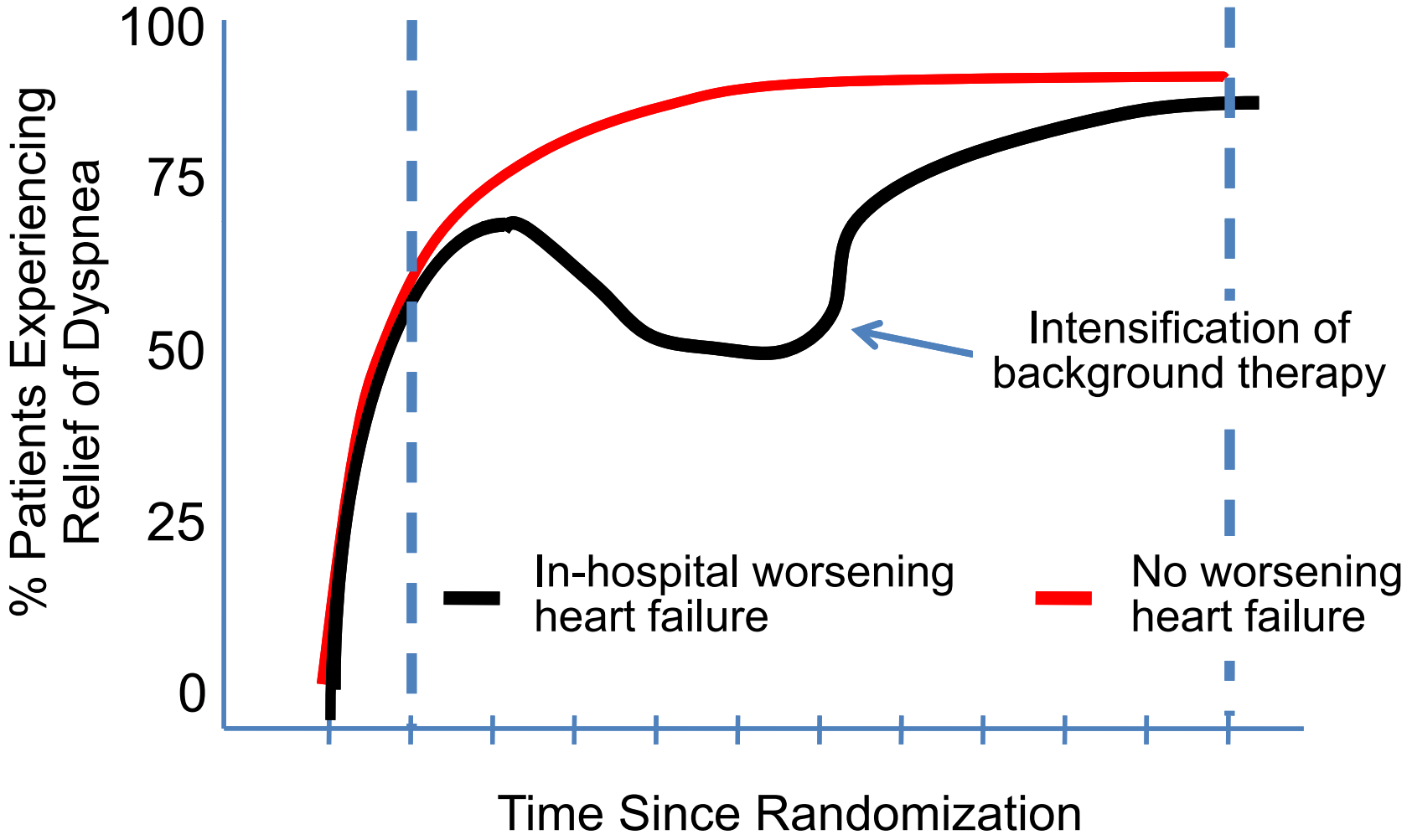
- Represents a meaningfully unfavorable change in clinical status, signifying instability in the patient's clinical course.

- Leads to intensification of therapy that may distort identification and interpretation of a treatment effect.

In-Hospital Worsening Heart Failure Indicates an Unfavorable Clinical Course



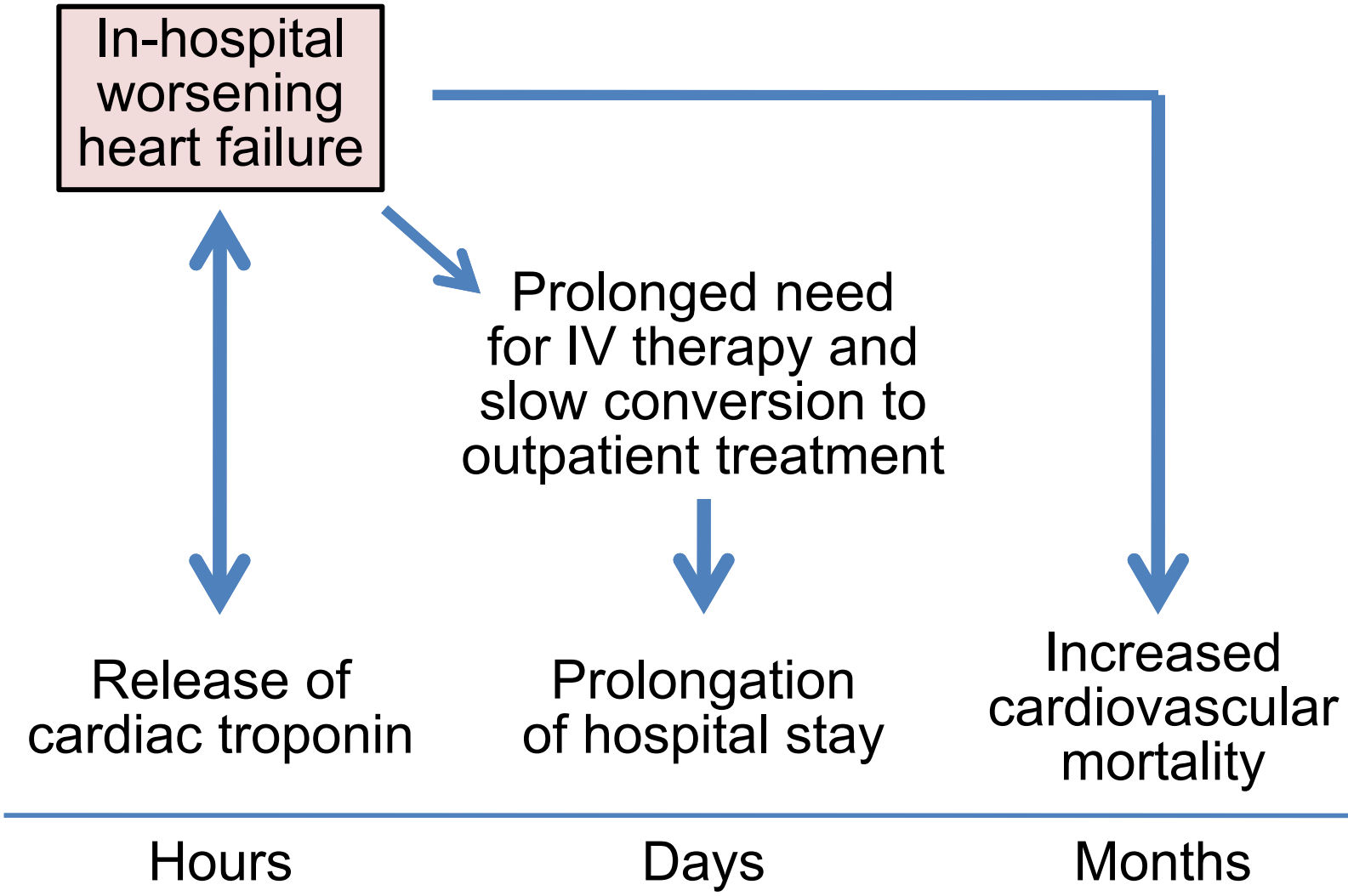
In-Hospital Worsening Heart Failure Indicates an Unfavorable Clinical Course



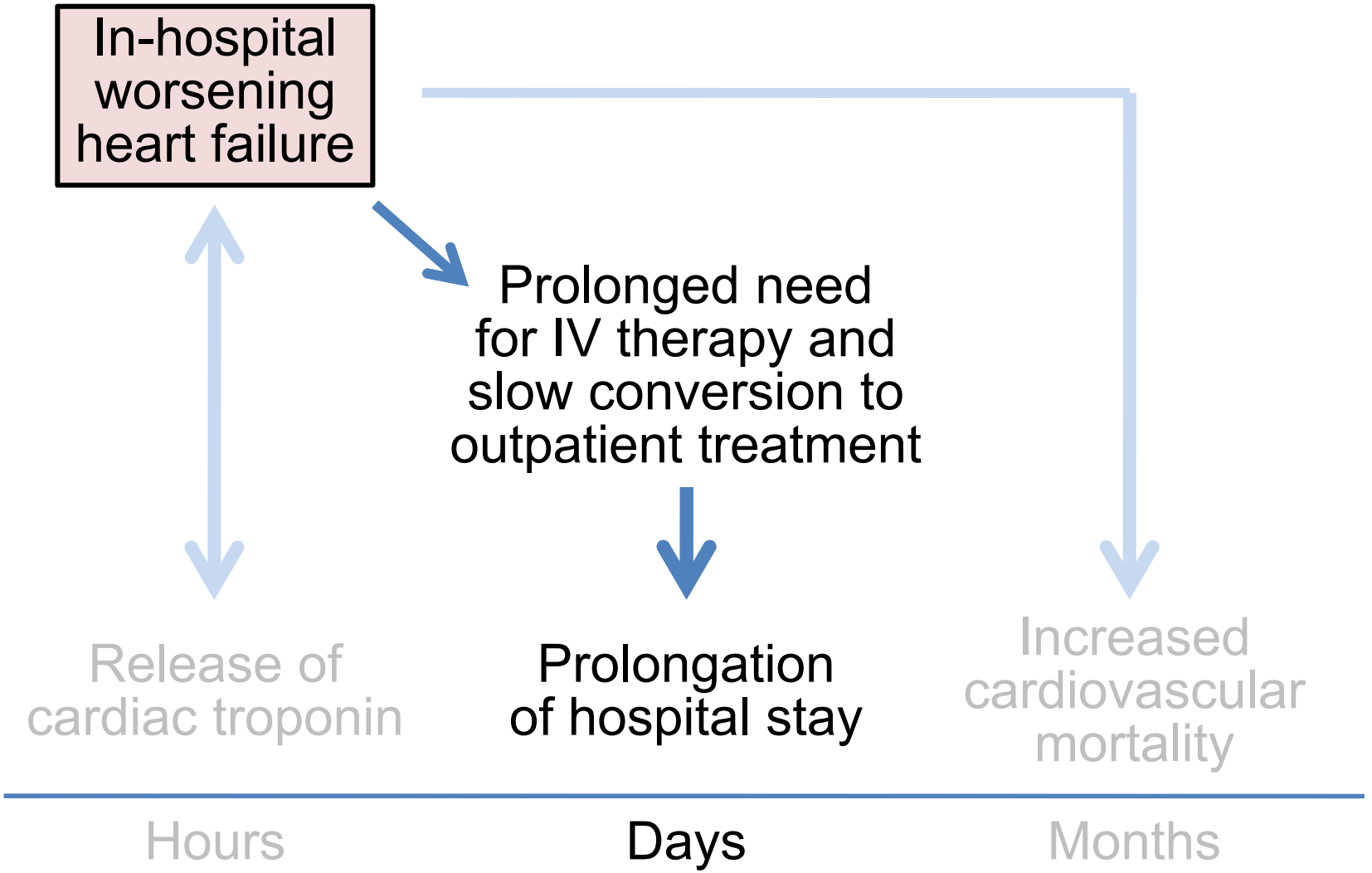
Why Do We Need to Focus on In-Hospital Worsening Heart Failure?

- Represents a meaningfully unfavorable change in clinical status, signifying instability in the patient's clinical course.
- Leads to intensification of therapy that may distort identification and interpretation of a treatment effect.
- May adversely influence the clinical course of patients.

Clinical Associations of In-Hospital Worsening Heart Failure



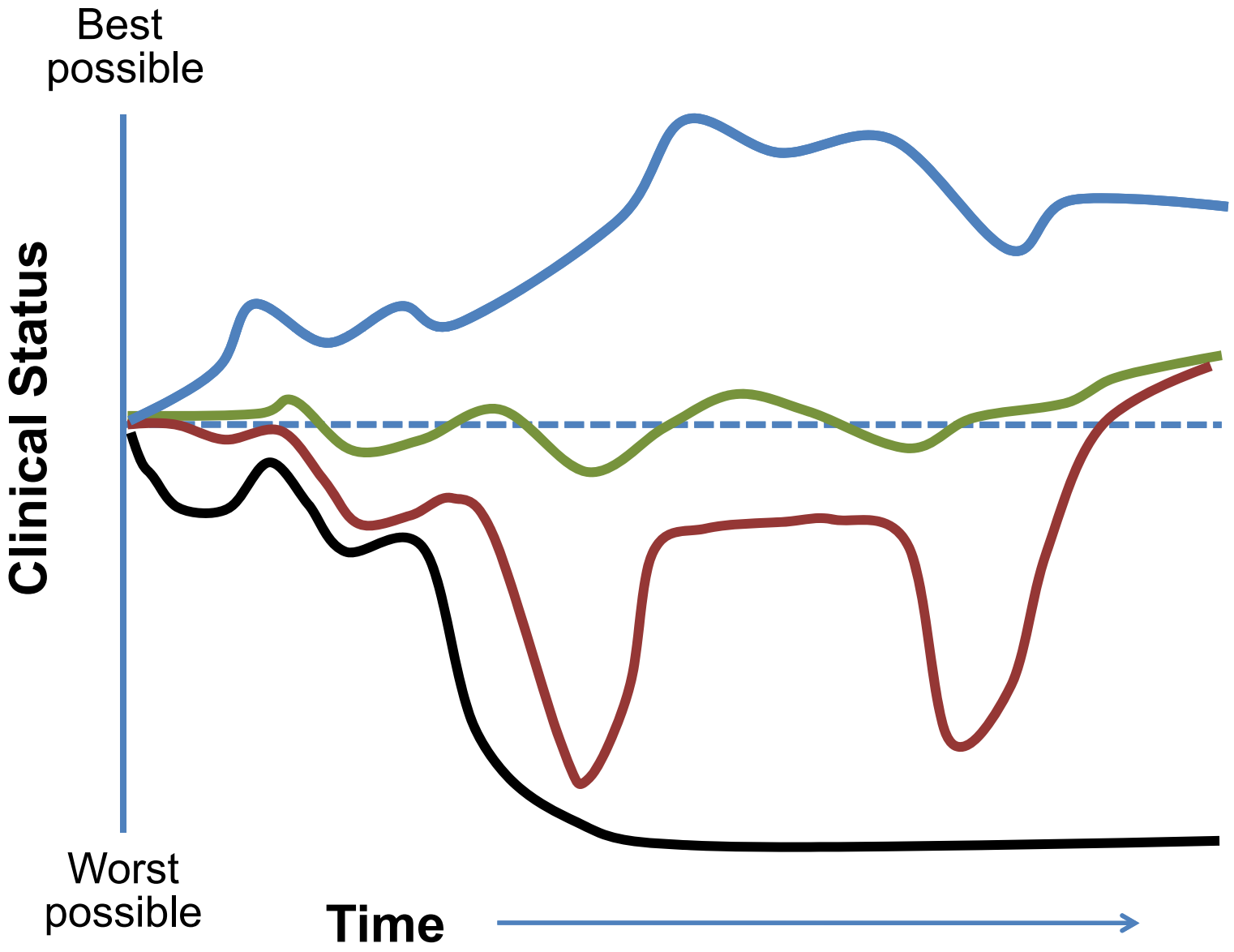
Worsening Heart Failure Reflects ***Treatment Failure*** on Conventional Therapy



In-Hospital Worsening Heart Failure Has Been Analyzed as a Treatment Failure

	Drug	In-hospital worsening heart failure incorporated into symptom endpoint
EVEREST	Tolvaptan	No
ASCEND	Nesiritide	No
VERITAS	Tezosentan	Worst rank or score
PROTECT	Rolofylline	Worst rank or score
REVIVE	Levosimendan	Worst rank or score
RELAX-AHF	Serelaxin	Worst rank or score
TRUE-AHF	Ularitide	Worst rank or score

Evaluating the Clinical Course of Patients



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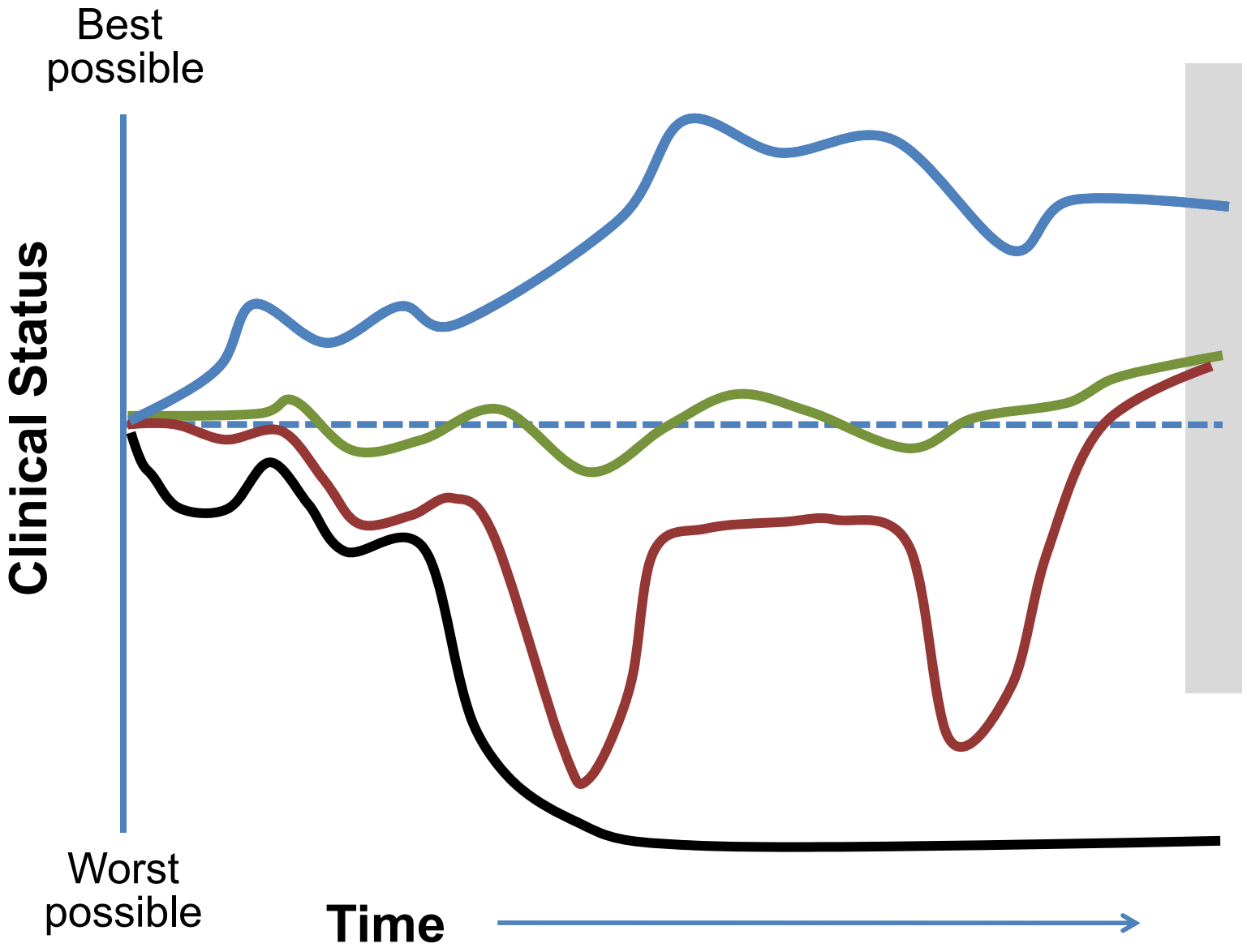
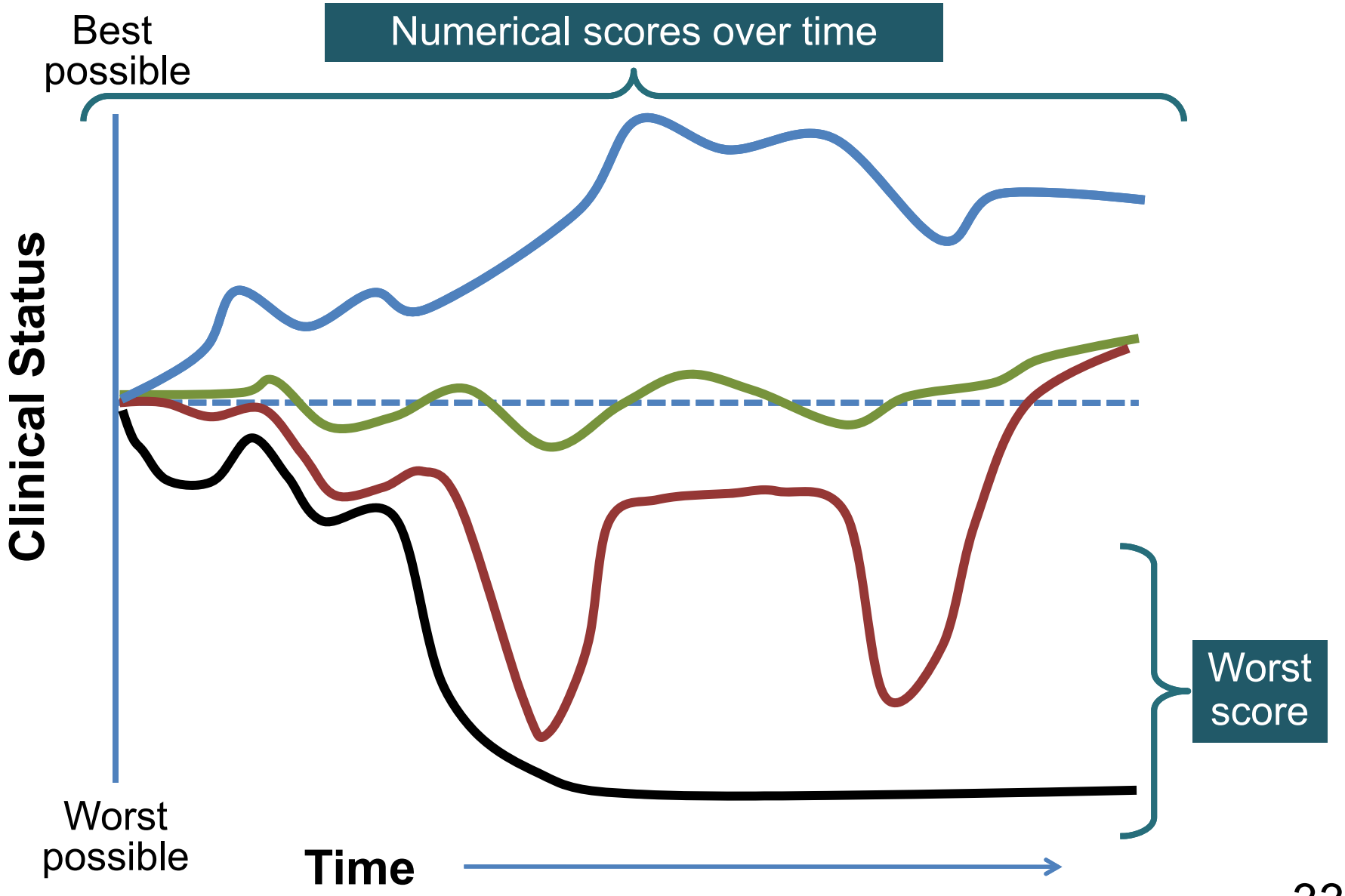
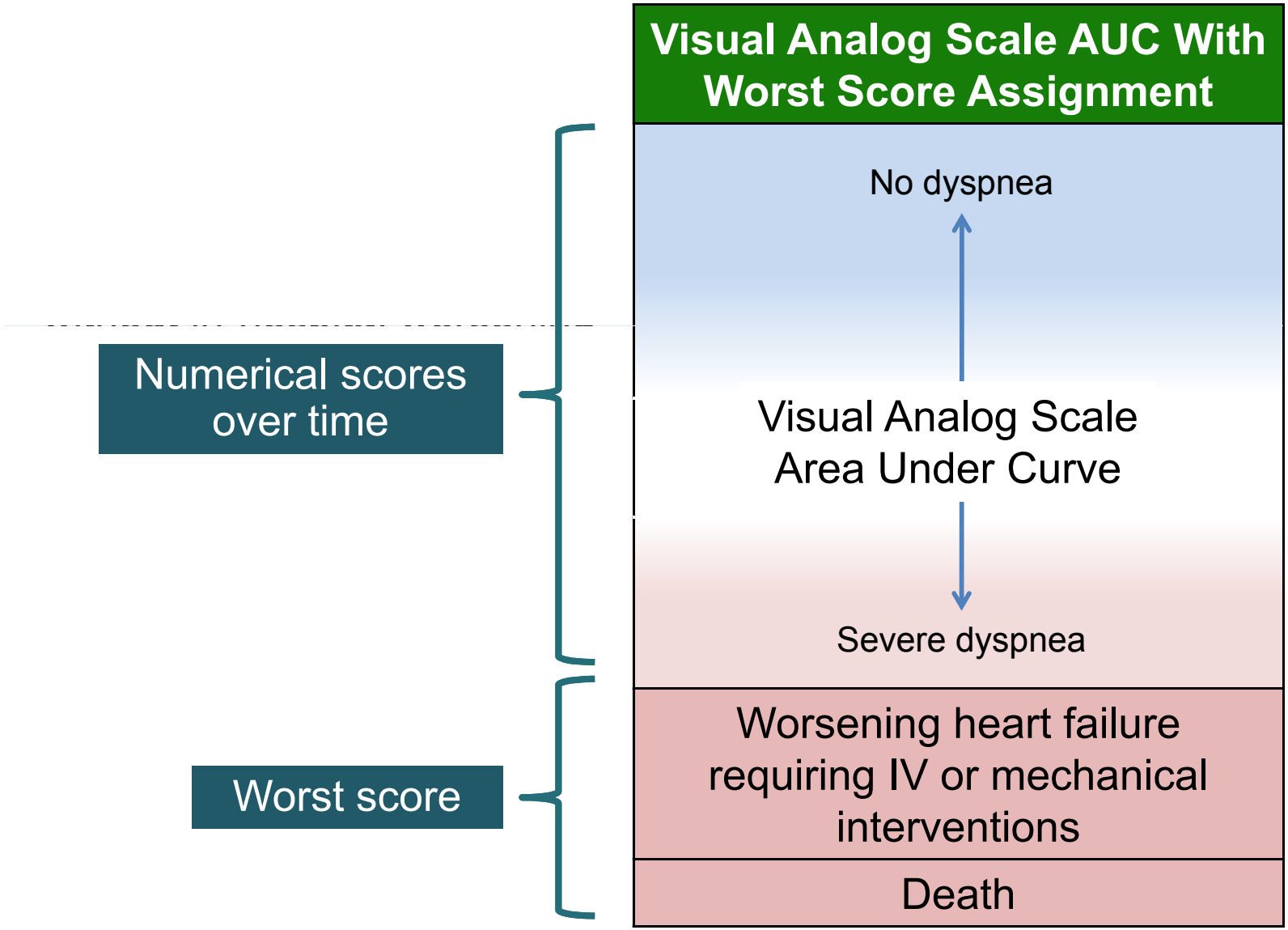


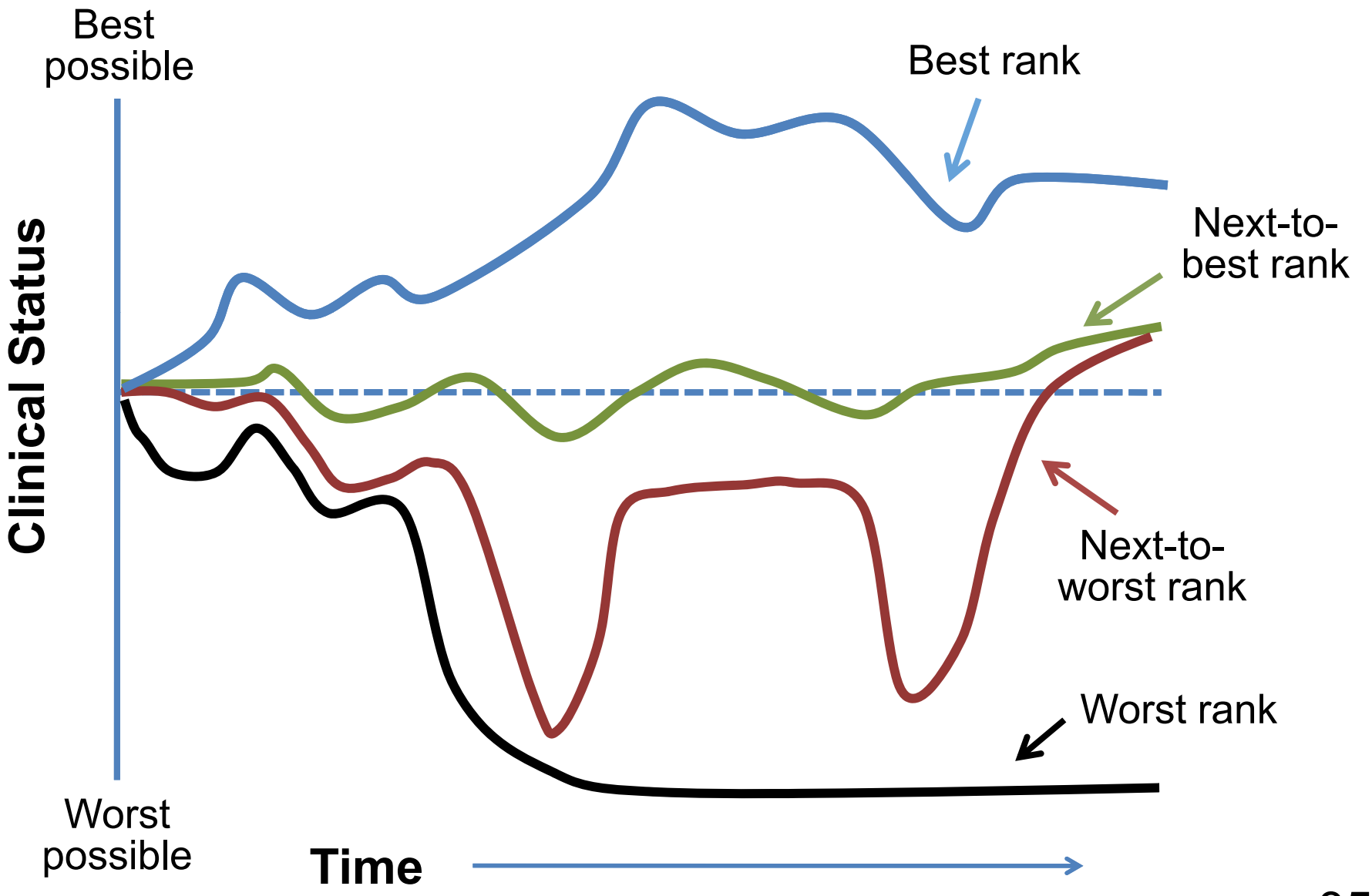
Numerical Assessment of Clinical Course



Visual Analog Scale Area Under Curve



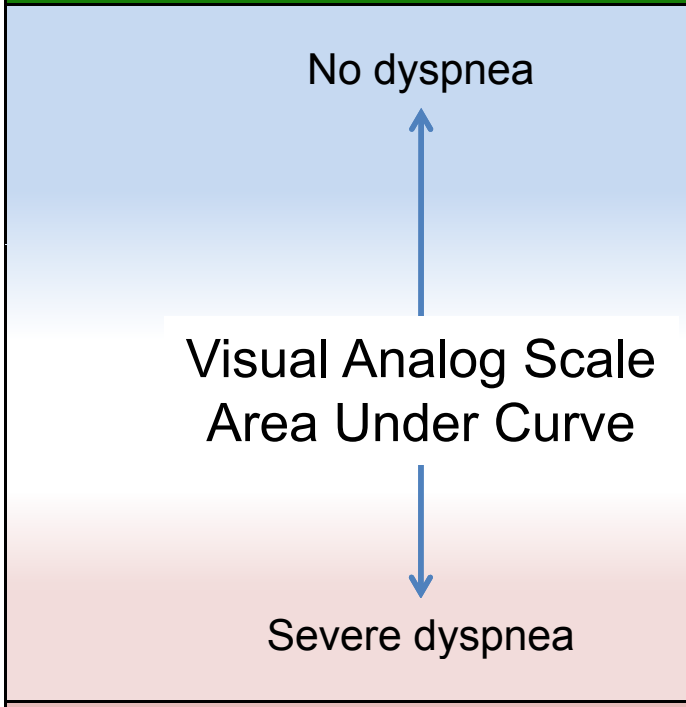
Ranking the Clinical Course of Patients



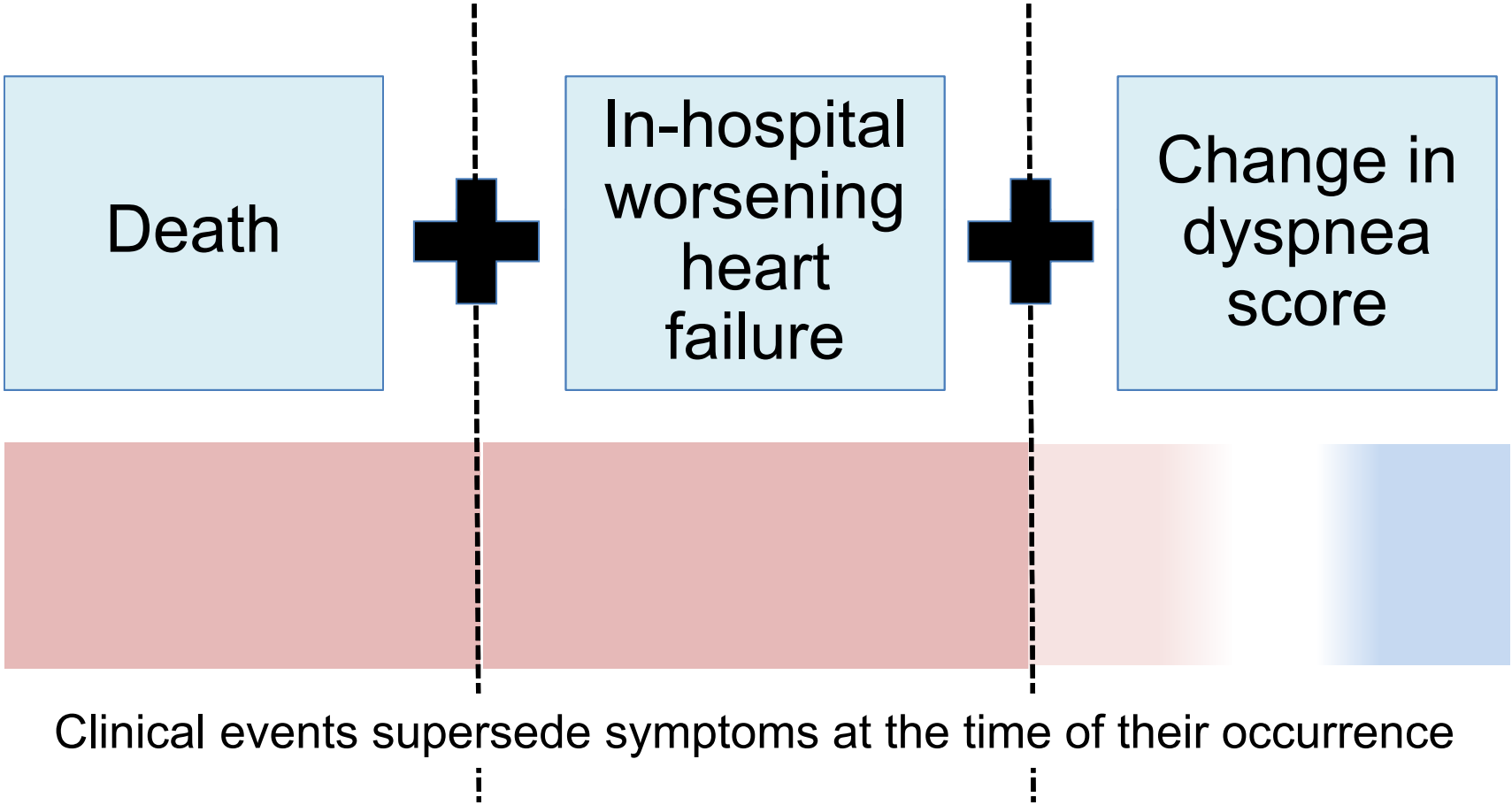
Clinical Composite (Acute Heart Failure)

Clinical Composite (Chronic Heart Failure)	Clinical Composite (Acute Heart Failure)
Moderate or marked improvement in clinical status at all planned assessments without hospitalization for heart failure or death	Moderate or marked improvement in symptoms at all planned assessments without in-hospital worsening heart failure or death
Modest improvement or worsening in clinical status	Modest improvement or worsening of symptoms
Moderate or marked worsening of clinical status at any planned assessment	Moderate or marked worsening of symptoms at any planned assessment
Hospitalization for heart failure requiring IV or mechanical interventions	Unresponsive or worsening heart failure (in-hospital) requiring IV or mechanical interventions
Death	Death

Composite Endpoints in Acute Heart Failure

Visual Analog Scale With Worst Score Assignment	Clinical Composite (Acute Heart Failure)
	Moderate or marked improvement in symptoms at all planned assessments without in-hospital worsening heart failure or death
	Modest improvement or worsening of symptoms
	Moderate or marked worsening of symptoms at any planned assessment
Worsening heart failure requiring IV or mechanical interventions	Unresponsive or worsening heart failure requiring IV or mechanical interventions
Death	Death

Visual Analog Scale Area Under the Curve Is a Composite Endpoint



RELAX-AHF Trial Design and Primary Endpoint Results

Olga Santiago, MD

Executive Global Program Head,
Critical Care
Novartis Pharmaceuticals Corporation

Overview of Presentation

- Pre-RELAX-AHF and RELAX-AHF Trials
  - Study design
- RELAX-AHF Trial
  - Primary endpoints
    - Visual Analog Scale Area Under the Curve
    - Likert scale analysis of early responders

Serelaxin Efficacy Program

RELAX-AHF

Near identical eligibility criteria, study design and efficacy endpoints

Pre-RELAX-AHF and RELAX-AHF: Eligibility Criteria

Key Inclusion Criteria

- Hospitalized for acute heart failure
  - Dyspnea at rest or minimal exertion
  - Pulmonary congestion on chest x-ray
  - BNP ≥350 or NT-pro-BNP ≥1400 pg/mL
- Received ≥40 mg IV furosemide (or equivalent) from time of initial clinical presentation to the start of screening
- Systolic blood pressure >125 mmHg
- Randomized within 16 hours from initial clinical presentation
- Impaired renal function on admission (eGFR 30-75 mL/min/1.73 m^2)

Key Exclusion Criteria

- Current or planned treatment with any IV therapies [i.e. other vasodilators, (nesiritide), positive inotropic agents and vasopressors] or mechanical circulatory, renal, or ventilatory support, with the exception of IV furosemide (or equivalent), or of IV nitrates if patient has screening SBP >150 mmHg

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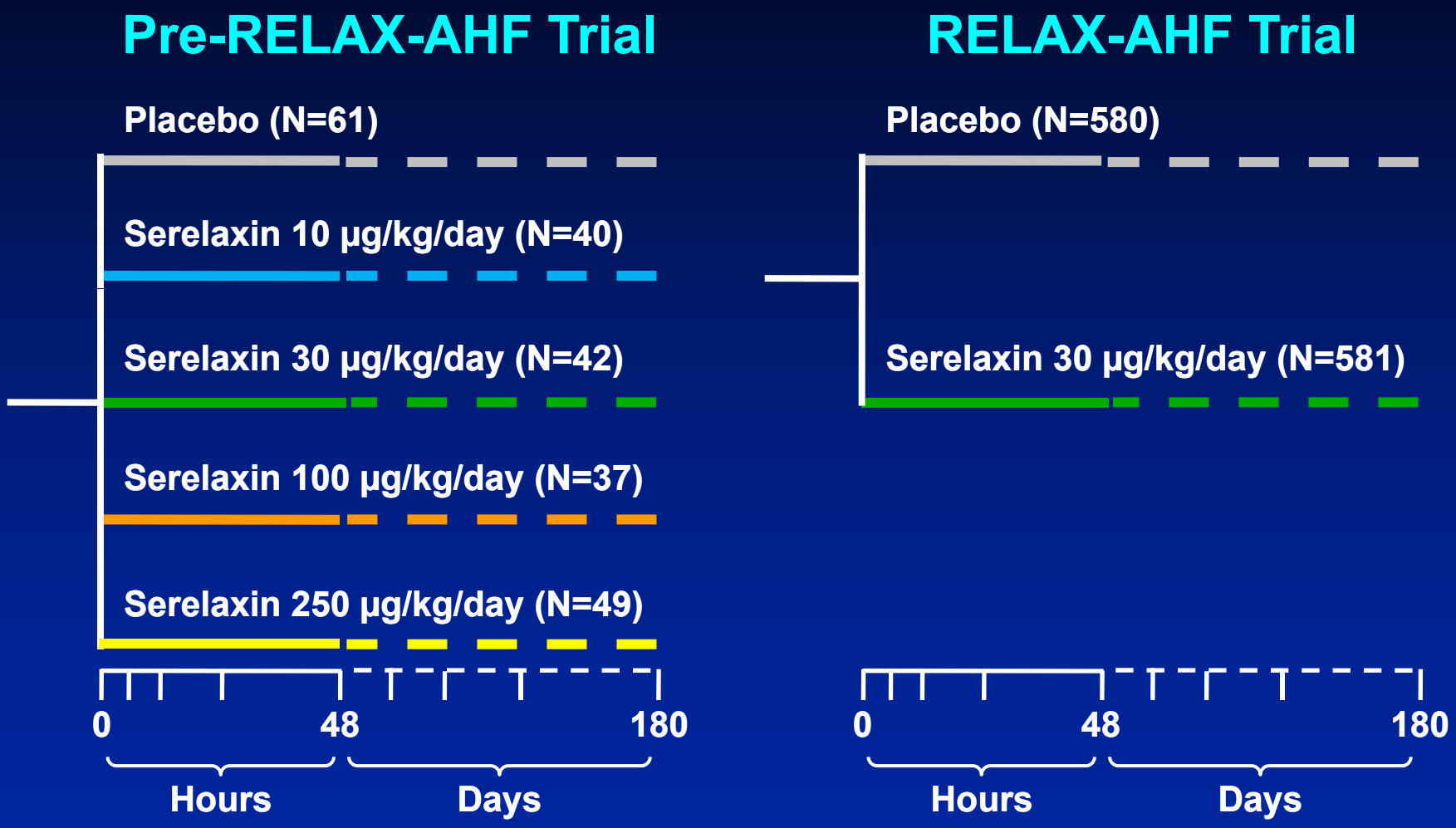
Pre-RELAX-AHF and RELAX-AHF: Study Designs



Pre-RELAX-AHF and RELAX-AHF: Efficacy Endpoints

Pre-RELAX-AHF Trial

- Visual Analog Scale Area Under the Curve during first 5 days
- Likert scale analysis of early responders during first 24 hours
- Incidence of worsening heart failure, or death at 5 days
- Length of index hospital stay
- Days alive and out of hospital through Day 60
- Cardiovascular death or hospitalization for heart or renal failure through Day 60
- Cardiovascular death through Day 180

RELAX-AHF Trial

- Visual Analog Scale Area Under the Curve during first 5 days
- Likert scale analysis of early responders during first 24 hours
- Incidence of worsening heart failure, rehospitalization or death at 5 and 14 days
- Length of index hospital stay
- Days alive and out of hospital through Day 60
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- Cardiovascular death through Day 180

Pre-RELAX-AHF and RELAX-AHF: Efficacy Endpoints

Pre-RELAX-AHF Trial	RELAX-AHF Trial
• Visual Analog Scale Area Under the Curve during first 5 days	• Visual Analog Scale Area Under the Curve during first 5 days
• Likert scale analysis of early responders during first 24 hours	• Likert scale analysis of early responders during first 24 hours
• Incidence of worsening heart failure, or death at 5 days	• Incidence of worsening heart failure, rehospitalization or death at 5 and 14 days
• Length of index hospital stay	• Length of index hospital stay
• Days alive and out of hospital through Day 60	• Days alive and out of hospital through Day 60
• Cardiovascular death or hospitalization for heart or renal failure through Day 60	• Cardiovascular death or hospitalization for heart or renal failure through Day 60
• Cardiovascular death through Day 180	• Cardiovascular death through Day 180

Pre-RELAX-AHF and RELAX-AHF: Efficacy Endpoints

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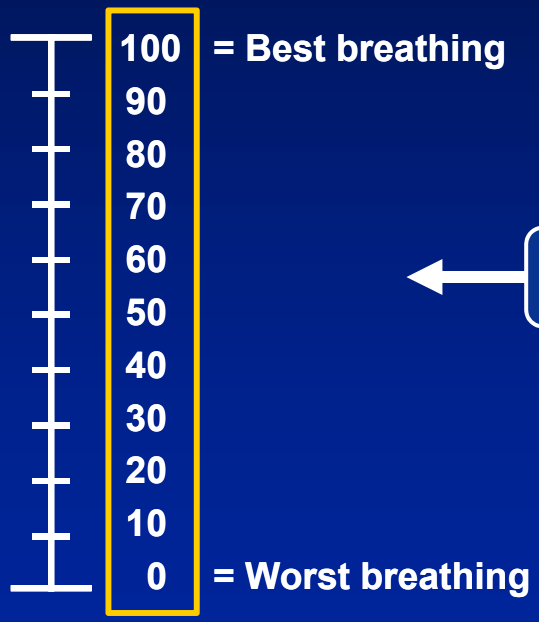
Primary and key secondary

RELAX-AHF: Design of Primary Endpoints

Visual Analog Scale Area Under the Curve

Improvement and worsening during first 5 days



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Likert Scale Analysis of Early Responders

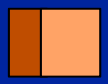
Moderate or marked improvement at 6h *and* 12h *and* 24h

- 3 = Markedly better
- 2 = Moderately better
- 1 = Minimally better
- 0 = No change
- -1 = Minimally worse
- -2 = Moderately worse
- -3 = Markedly worse

Worsening heart failure, rehospitalization for heart failure and death within 5 days were assigned worst observed score

RELAX-AHF: Scope of Primary Endpoints

	Day 1	Day 2	Day 3	Day 4	Day 5
Meaningful improvement of dyspnea	6 12 24h				
Minimal or no changes in dyspnea					
Meaningful worsening of dyspnea					
In-hospital worsening heart failure or death					



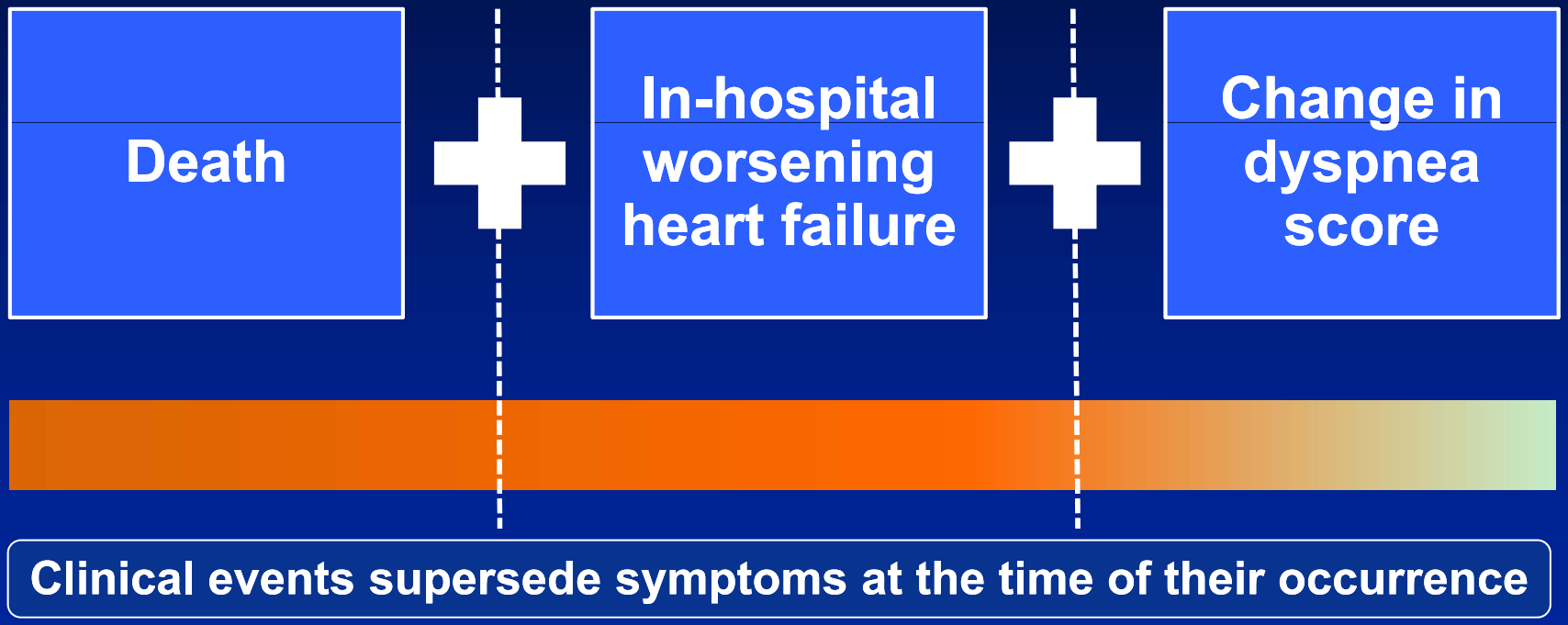
Likert analysis of early responders

RELAX-AHF: Scope of Primary Endpoints

	Day 1	Day 2	Day 3	Day 4	Day 5
Meaningful improvement of dyspnea					
Minimal or no changes in dyspnea					
Meaningful worsening of dyspnea					
In-hospital worsening heart failure or death					

Visual Analog Scale Area Under the Curve

Visual Analog Scale Area Under the Curve Was Designed as a Composite Endpoint

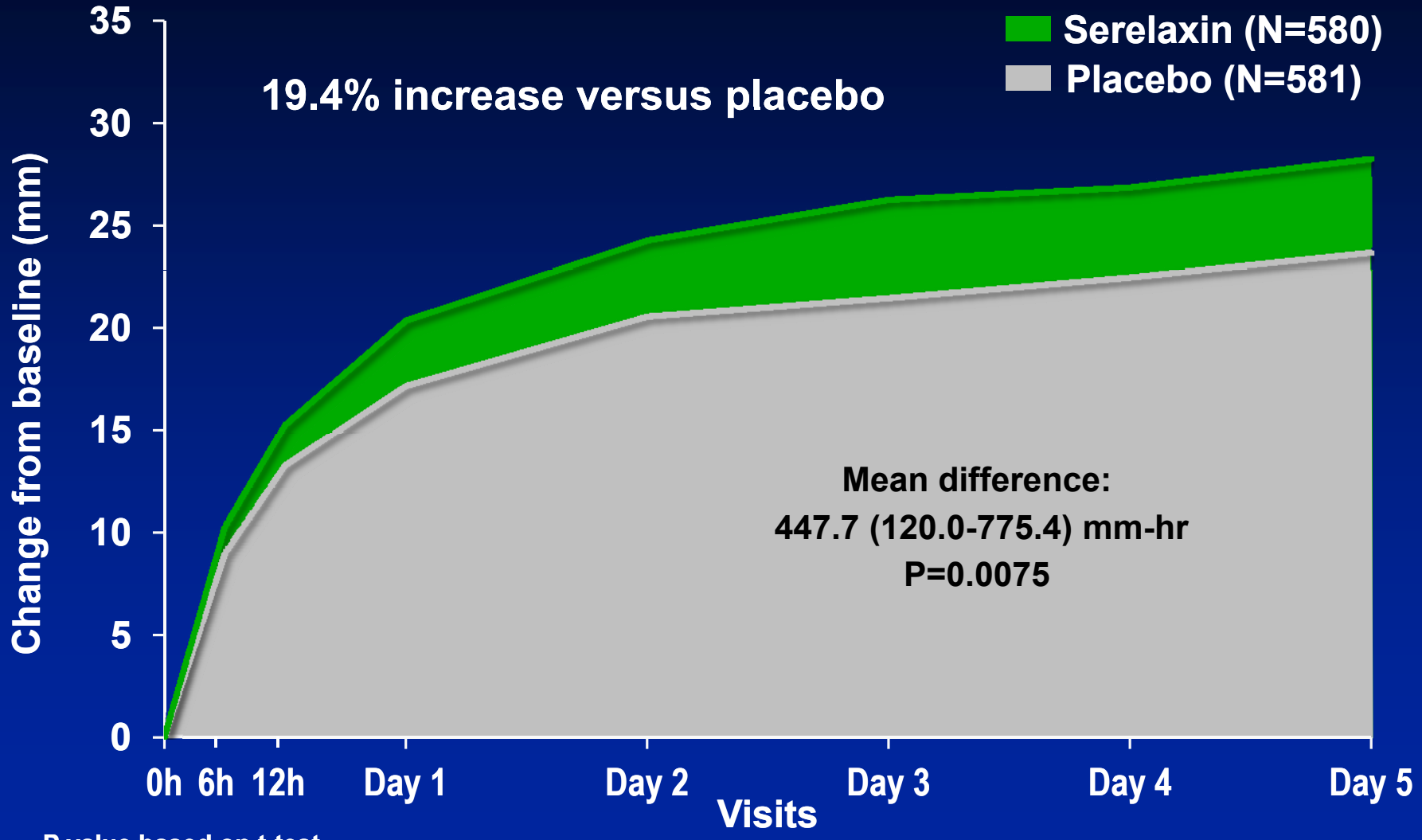


RELAX-AHF: Baseline Characteristics

	Placebo (N=580)	Serelaxin (N=581)
Age (years)	72.5	71.6
Systolic blood pressure at baseline (mmHg)	142	142
Heart rate at baseline (bpm)	80	79
eGFR (mL/min/1.73m^2)	53.3	53.7
NT-proBNP (pg/mL)	5003	5125
Proportion with LV ejection fraction < 40% (%)	55	55
Hospitalization for heart failure in the past year (%)	31	37*
Atrial fibrillation/atrial flutter at presentation (%)	42	40
Diabetes mellitus (%)	47	48
ACE inhibitor or angiotensin receptor blocker (%)	72	69
Beta-blocker (%)	70	67
Aldosterone antagonist (%)	30	33
IV nitrates at randomization (%)	7	7
Time from presentation to randomization (hr)	7.9	7.8

Unless otherwise stated, data shown are means, except for NT-proBNP (geometric mean); * P< 0.05 (nominal)

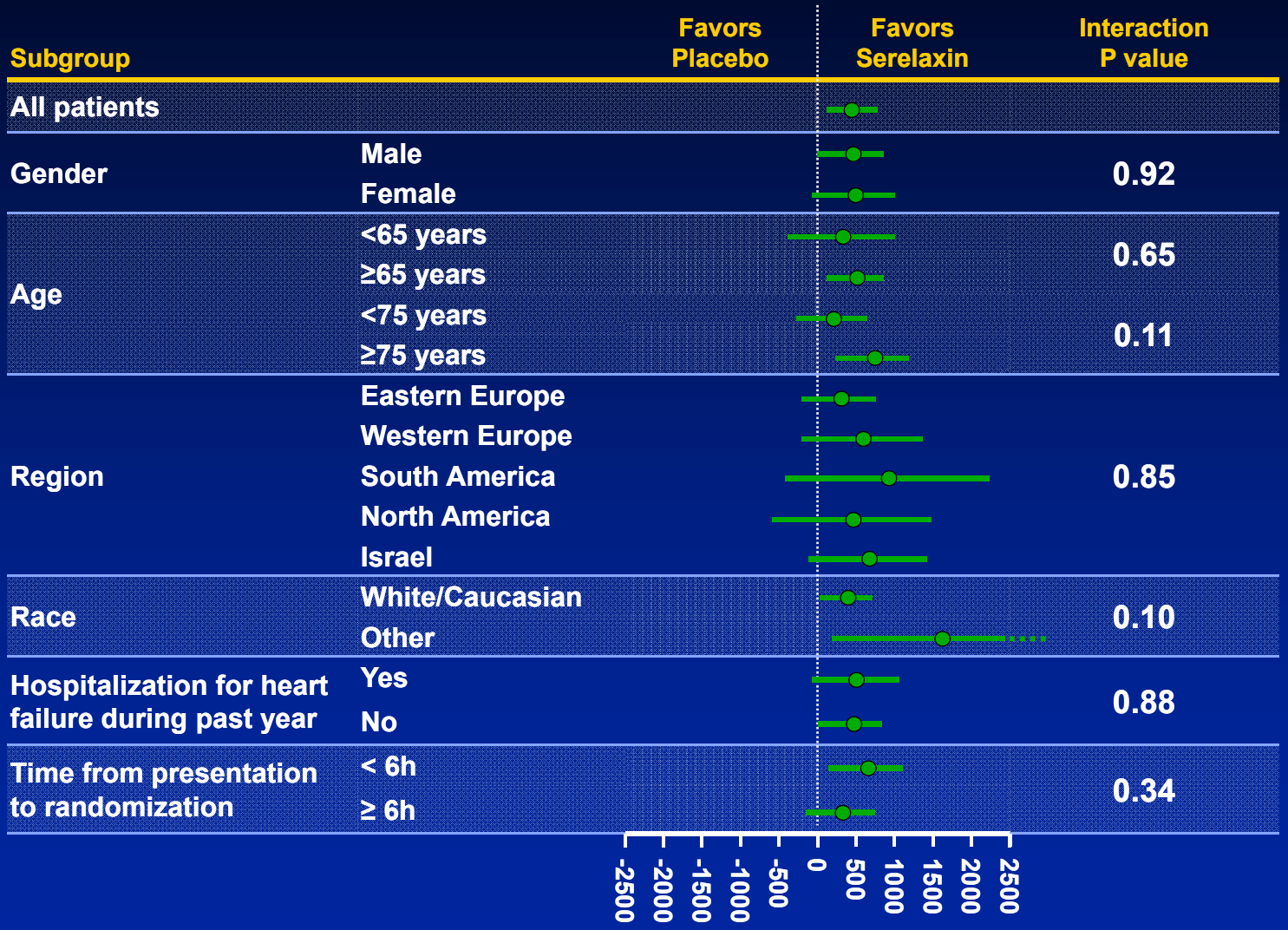
Primary Endpoint: Visual Analog Scale AUC Composite Through Day 5



P value based on t-test

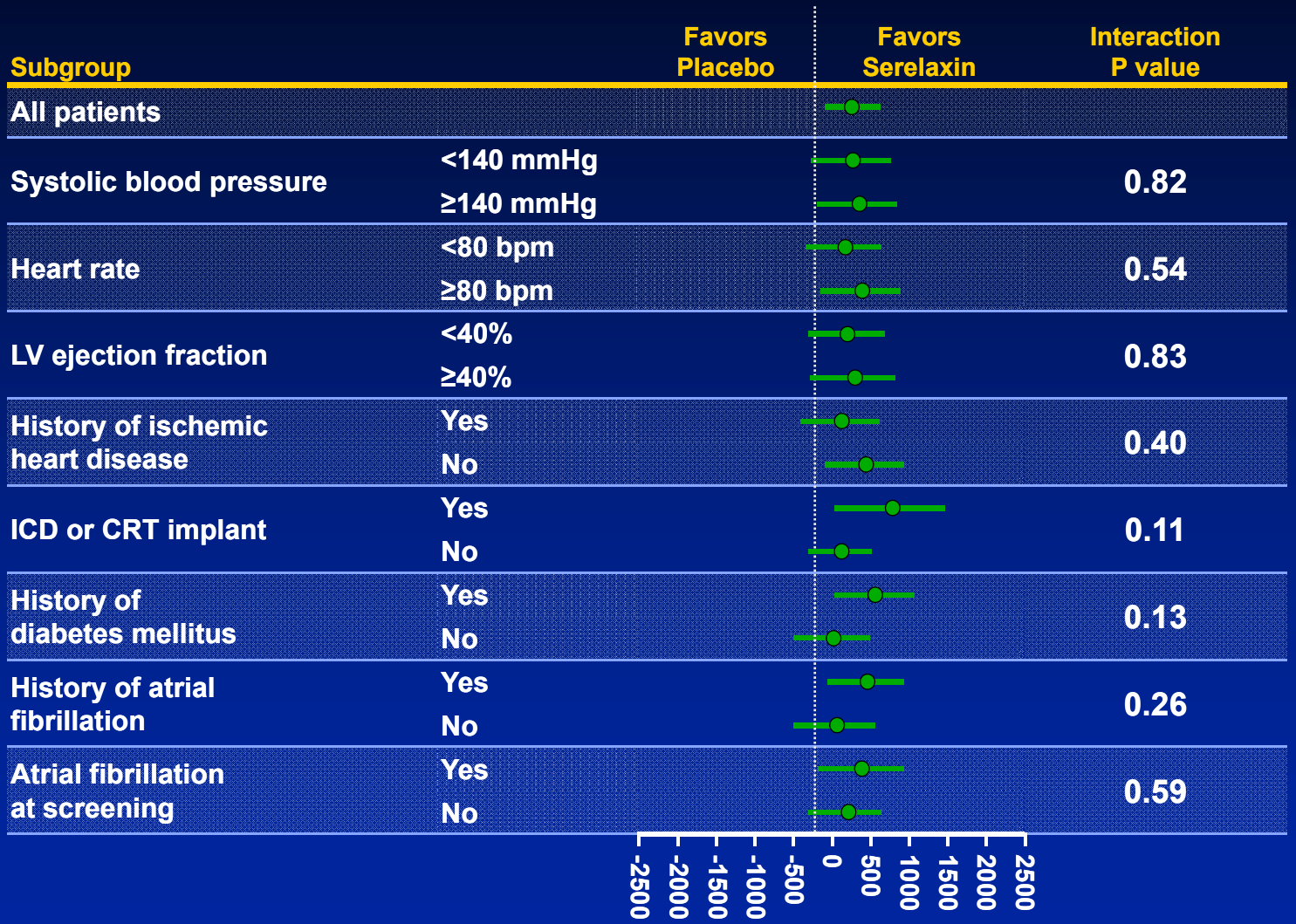
Teerlink et al. Lancet 2013;381:29–39

Primary Endpoint: Visual Analog Scale AUC Composite by Subgroups

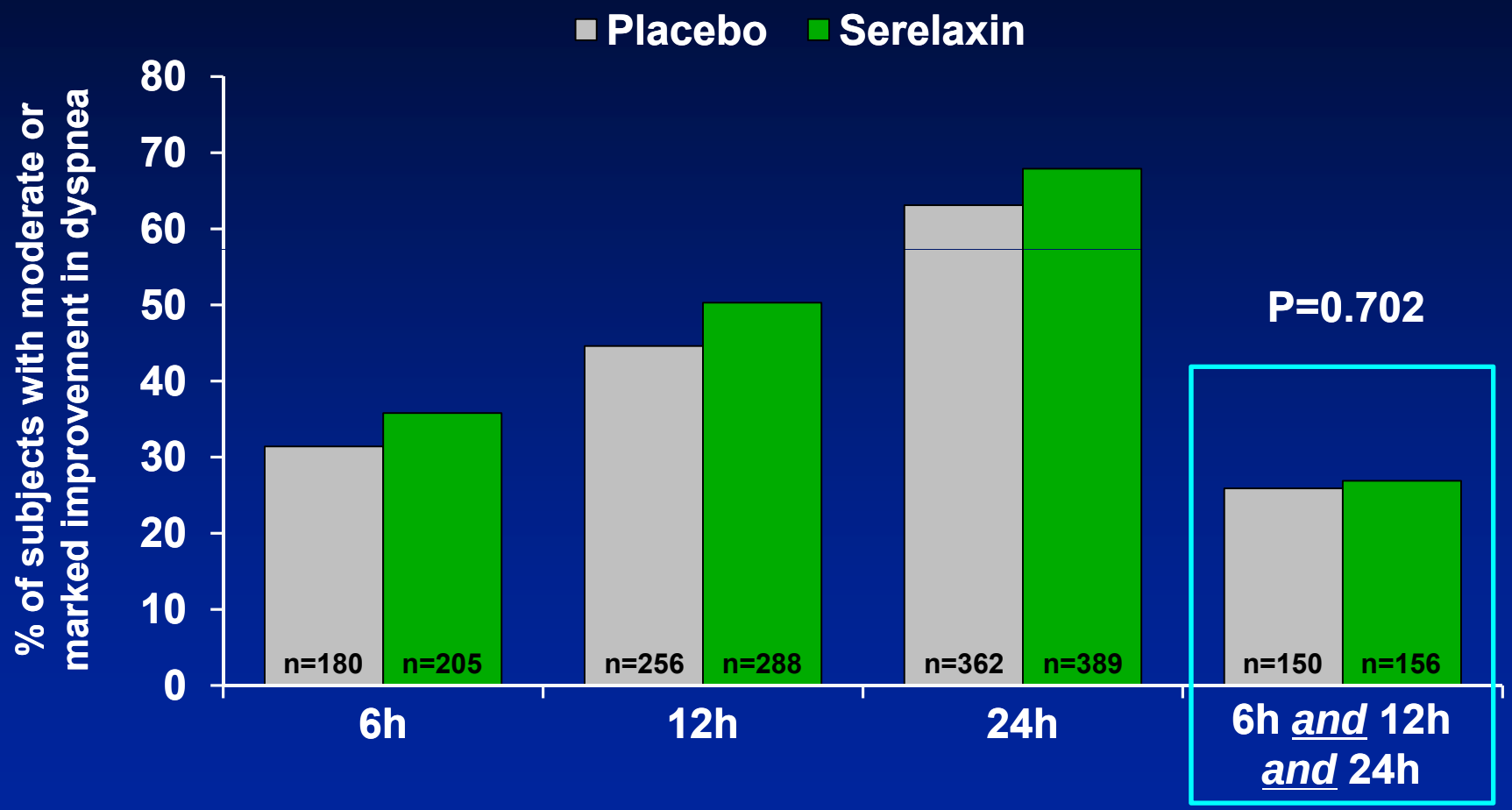


Metra M et al., J Am Coll Cardiol 2013, 61(2):196-206

Primary Endpoint: Visual Analog Scale AUC Composite by Subgroups



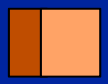
Primary Endpoint: Likert Scale Analysis of Early Responders



P value by chi-square test

RELAX-AHF: Scope of Primary Endpoints

	Day 1	Day 2	Day 3	Day 4	Day 5
Meaningful improvement of dyspnea	6 12 24h				
Minimal or no changes in dyspnea					
Meaningful worsening of dyspnea					
In-hospital worsening heart failure or death					



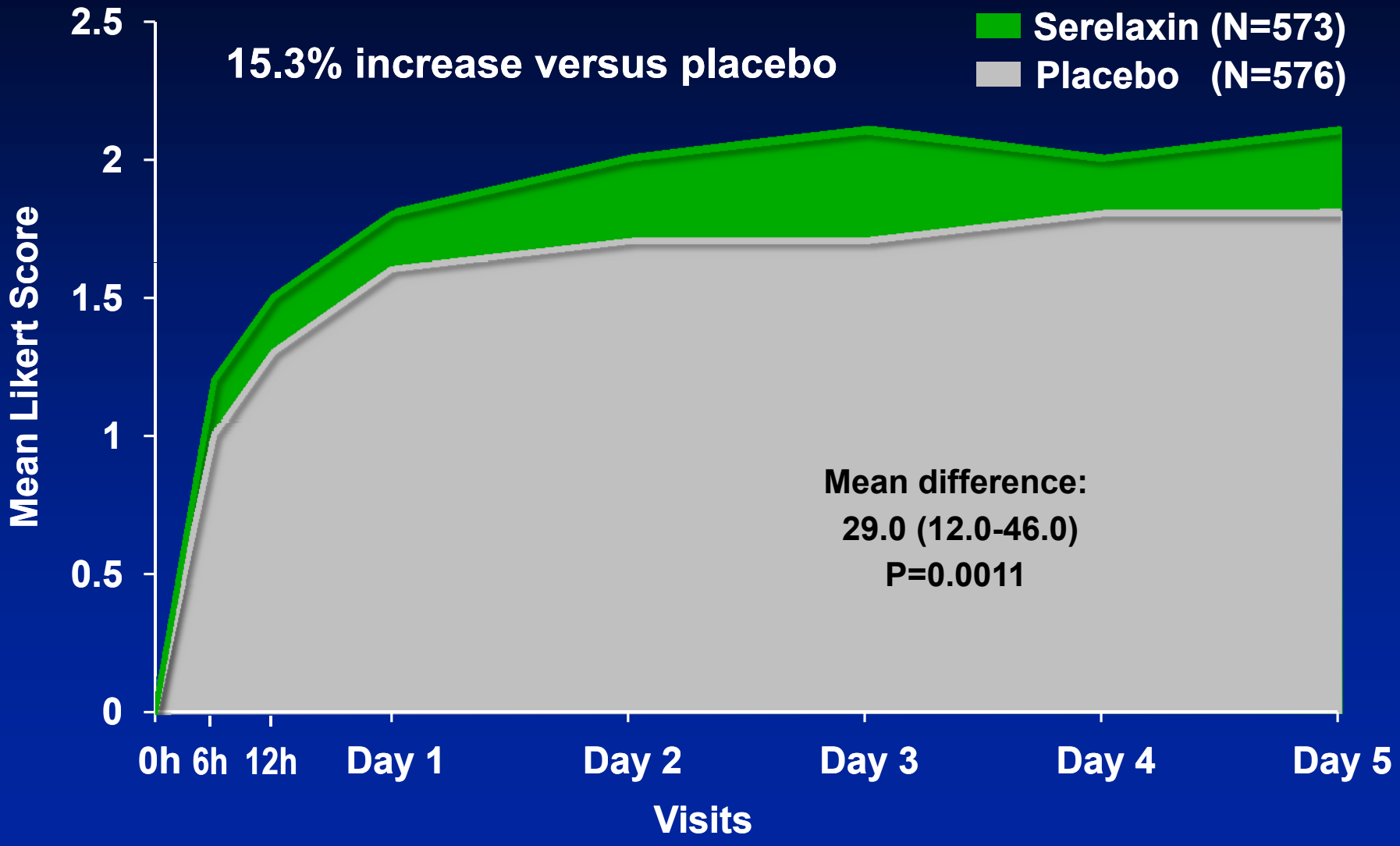
Likert analysis of early responders

RELAX-AHF: Scope of Primary Endpoints

	Day 1	Day 2	Day 3	Day 4	Day 5
Meaningful improvement of dyspnea					
Minimal or no changes in dyspnea					
Meaningful worsening of dyspnea					
In-hospital worsening heart failure or death					

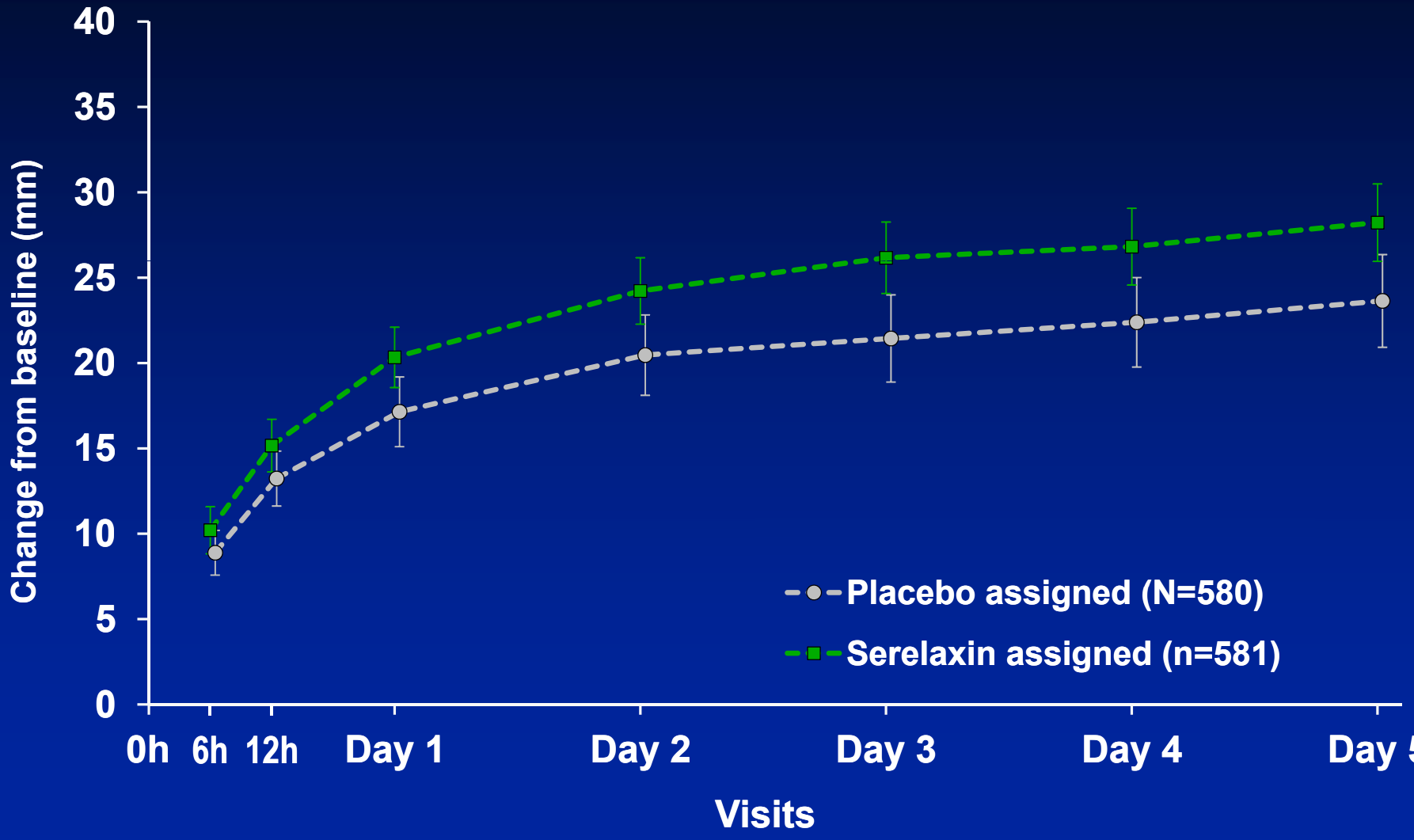
Likert Area Under the Curve: Improvement + worsening

Likert Analysis Using Full Scale and Worst Score Assignment for Worsening Events



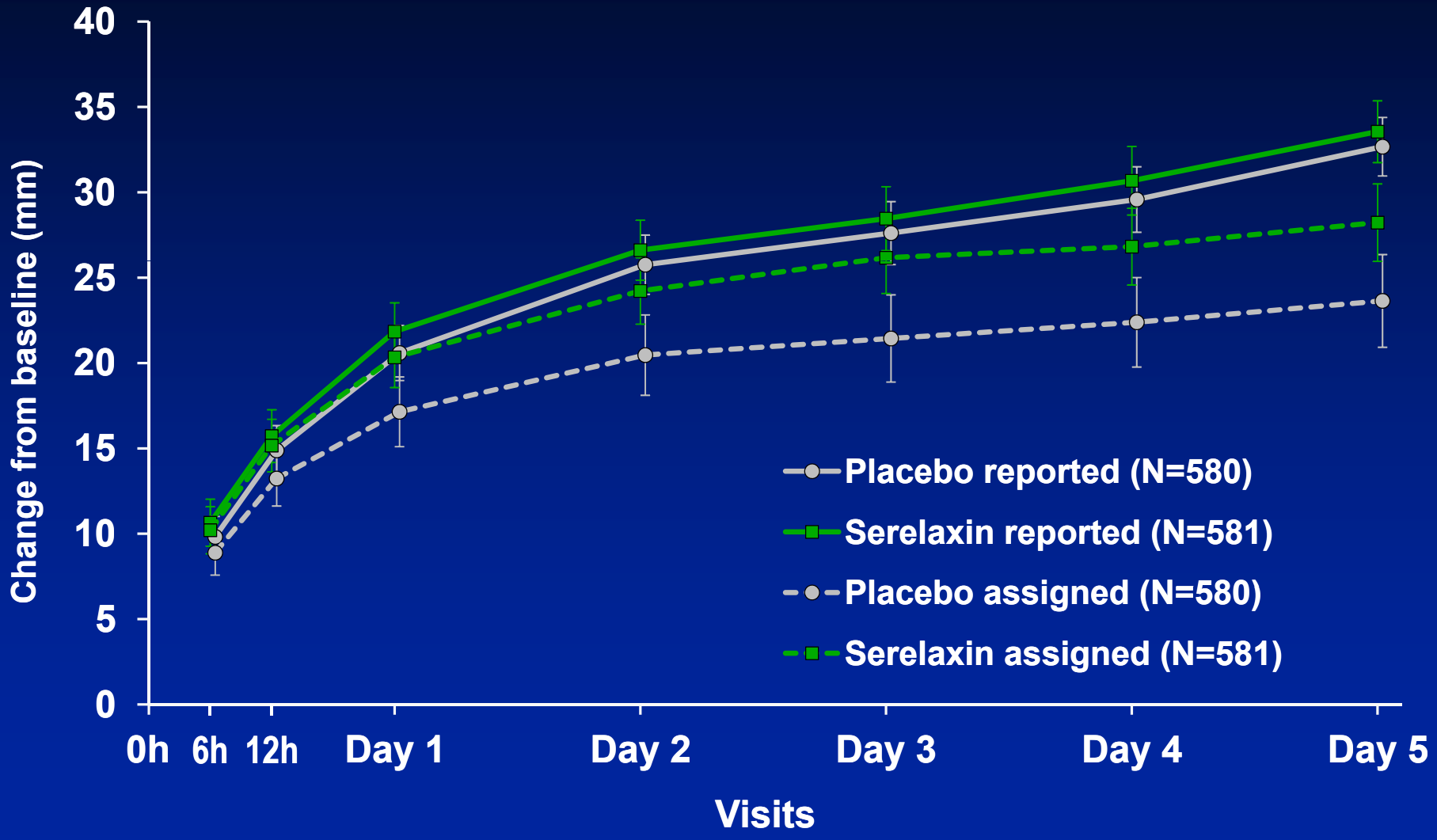
P value based on t-test

Visual Analog Scale With Worst Score Assignment for Worsening Events



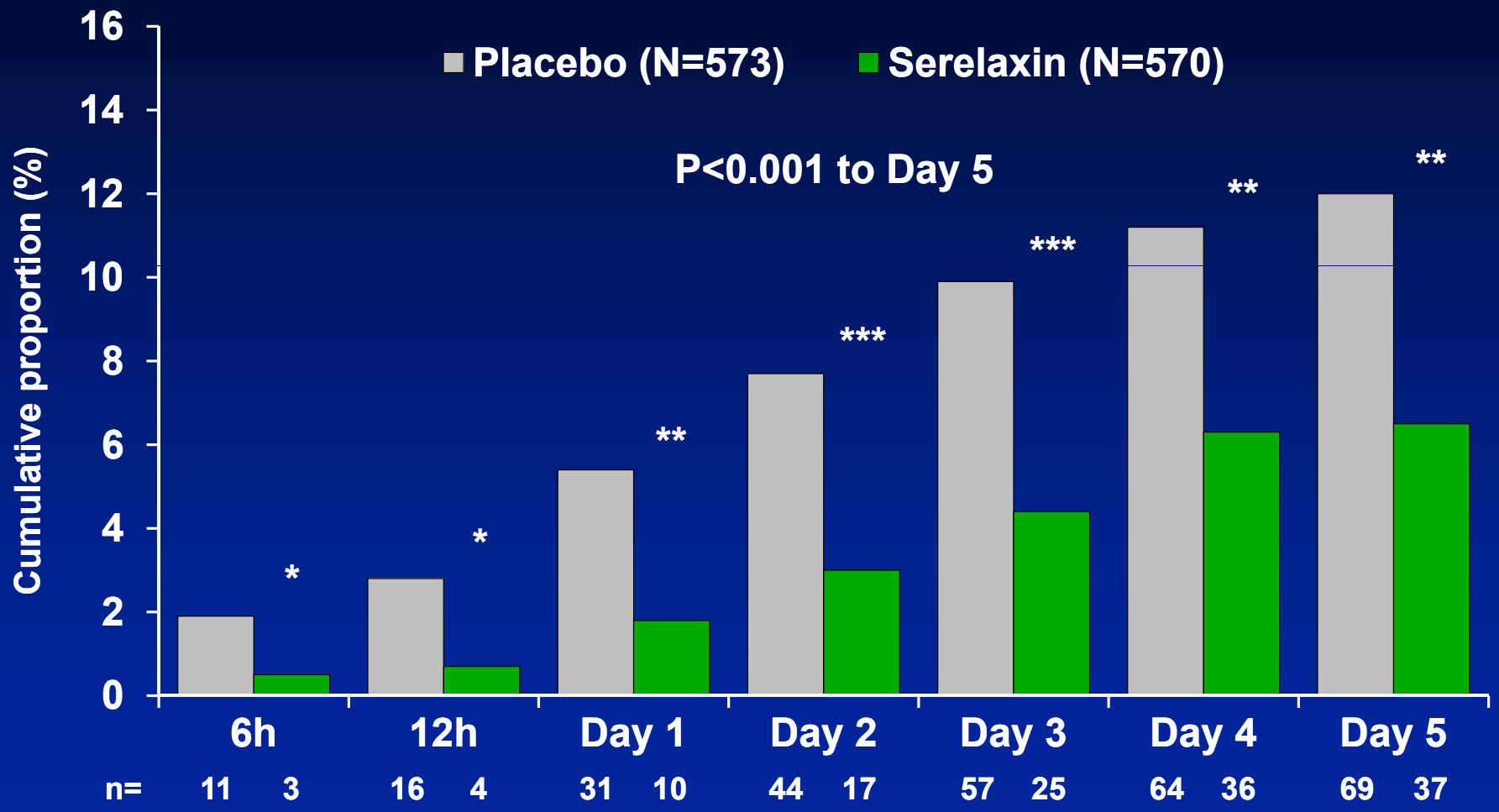
Data presented as mean ± 95% CI

Visual Analog Scale With and Without Worst Score Assignment for Worsening Events



Data presented as mean ± 95% CI

Incidence of In-Hospital Worsening Heart Failure or Death Through Day 5



* P<0.05; ** P<0.005; *** P<0.001 using logistic regression.
P value to Day 5 based on Wilcoxon test

Robustness of Analyses of In-Hospital Worsening Heart Failure as a Clinical Event

- Was in-hospital worsening heart failure adequately documented as an event?
- Was in-hospital worsening heart failure a clinically meaningful event?
- Why was worst score assigned to in-hospital worsening heart failure from the time of its occurrence?
- Was worsening heart failure specified as an exploratory (and not primary) endpoint?
- Was the effect of serelaxin on in-hospital worsening heart failure robust?

Robustness of Analyses of In-Hospital Worsening Heart Failure as a Clinical Event

- **Was in-hospital worsening heart failure adequately documented as an event?**
- **Was in-hospital worsening heart failure a clinically meaningful event?**
- **Why was worst score assigned to in-hospital worsening heart failure from the time of its occurrence?**
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- **Was the effect of serelaxin on in-hospital worsening heart failure robust?**

Definition of Worsening Heart Failure in RELAX-AHF

"Worsening heart failure is defined for this study as worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical, ventilatory or circulatory support."

"Such treatment can include the institution or uptitration of IV furosemide, IV nitrates or any other IV medication for heart failure, or institution of mechanical support such as mechanical ventilation, IABP, etc."

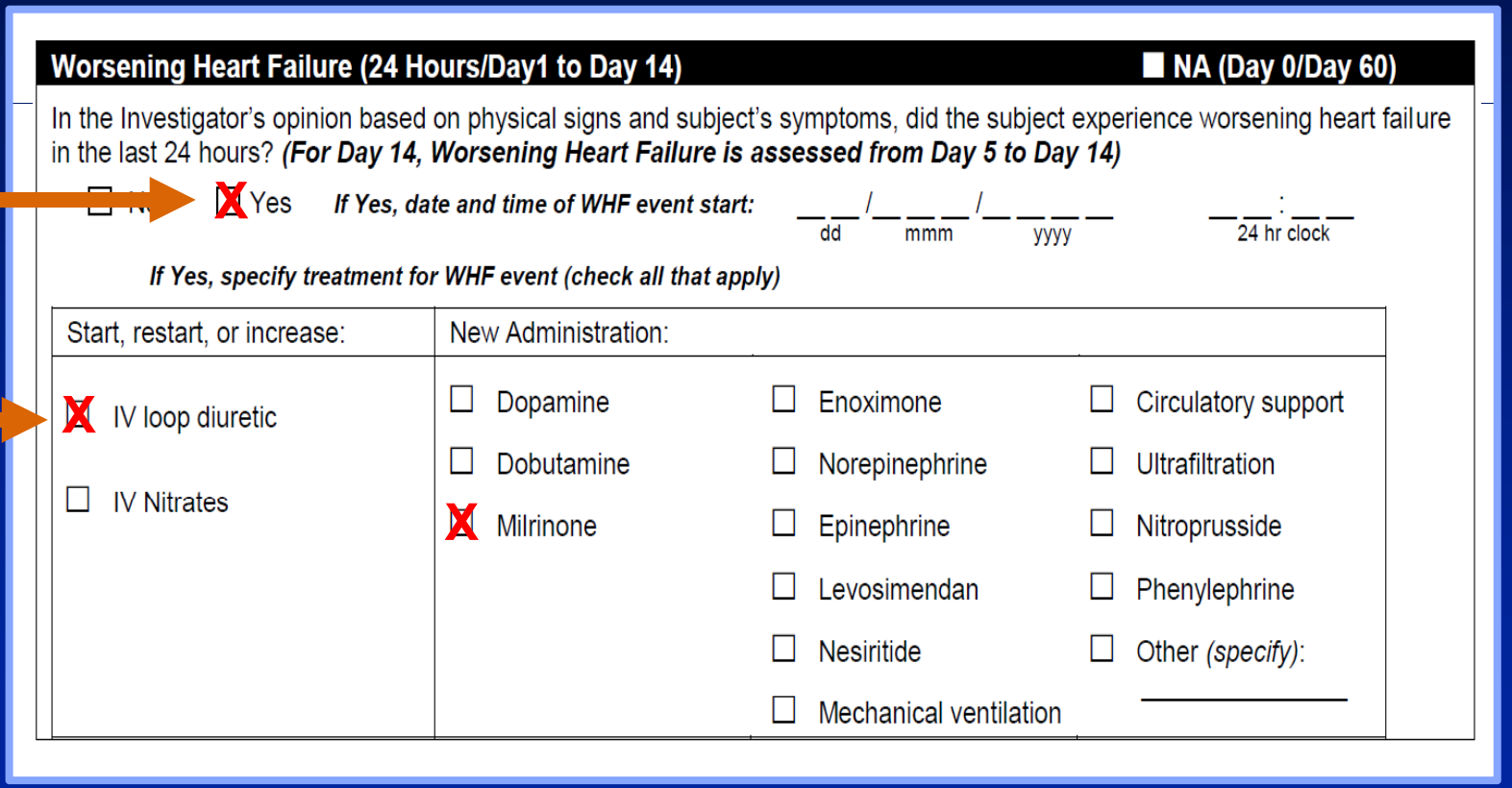
"It is important to note that medications for heart failure (such as IV treatment for hypertension control) can be added for reasons other than worsening heart failure."

RELAX-AHF: Identification of Worsening Heart Failure Events

1. **Patient reports worsening of clinical status**

2. **Clinician diagnoses worsening heart failure**

3. **Clinician responds by intensification of IV therapy**



Worsening Heart Failure (24 Hours/Day1 to Day 14) ☐ NA (Day 0/Day 60)

In the Investigator's opinion based on physical signs and subject's symptoms, did the subject experience worsening heart failure in the last 24 hours? ***(For Day 14, Worsening Heart Failure is assessed from Day 5 to Day 14)***

☐ N ☒ Yes ***If Yes, date and time of WHF event start:*** __ __ / __ __ __ / __ __ __ __ (dd / mmm / yyyy) __ __ : __ __ (24 hr clock)

If Yes, specify treatment for WHF event (check all that apply)

Start, restart, or increase:	New Administration:		
☒ IV loop diuretic	☐ Dopamine	☐ Enoximone	☐ Circulatory support
☐ IV Nitrates	☐ Dobutamine	☐ Norepinephrine	☐ Ultrafiltration
	☒ Milrinone	☐ Epinephrine	☐ Nitroprusside
		☐ Levosimendan	☐ Phenylephrine
		☐ Nesiritide	☐ Other *(specify)*: _____
		☐ Mechanical ventilation	

Was In-Hospital Worsening Heart Failure Verified as a Clinical Event?

- Adverse events were documented in 98 of 102 in-hospital worsening heart failure events
  - Included description, time and date of onset and offset, and treatment
- Treatments for in-hospital worsening heart failure were documented on the medication pages of the case report form

Worsening Heart Failure Events Were Described as Adverse Events

Total number of patients with worsening heart failure	102
Total number of patients whose in-hospital worsening heart failure was recorded as an adverse event	98* (96%)
Total number of adverse events related to in-hospital WHF	102**
Cardiac failure congestive	49
Dyspnea	23
Cardiac failure	11
Acute pulmonary edema	6
Cardiac failure acute	5
Acute left ventricular failure	1
Acute respiratory failure	1
Cardiogenic shock	1
Edema peripheral	1
Pulmonary congestion	1
Pulmonary edema	1
Respiratory distress	1
Respiratory failure	1

* Within 24 hours of WHF; ** 3 patients had multiple adverse events reported

Rescue Interventions Used to Respond to In-Hospital Worsening Heart Failure

	Placebo (N=580)	Serelaxin (N=581)
Number of patients who died or had in-hospital worsening or rehospitalization for HF through Day 5	69	37
IV inotropes and/or mechanical ventilation or circulatory support (± IV vasodilators ± IV diuretics)	14	7
IV vasodilators (± IV diuretics)	13	8
IV diuretics only	38	19

One patient on placebo experienced HF rehospitalization at Day 4
3 patients died prior to Day 5 without preceding WHF in each treatment group

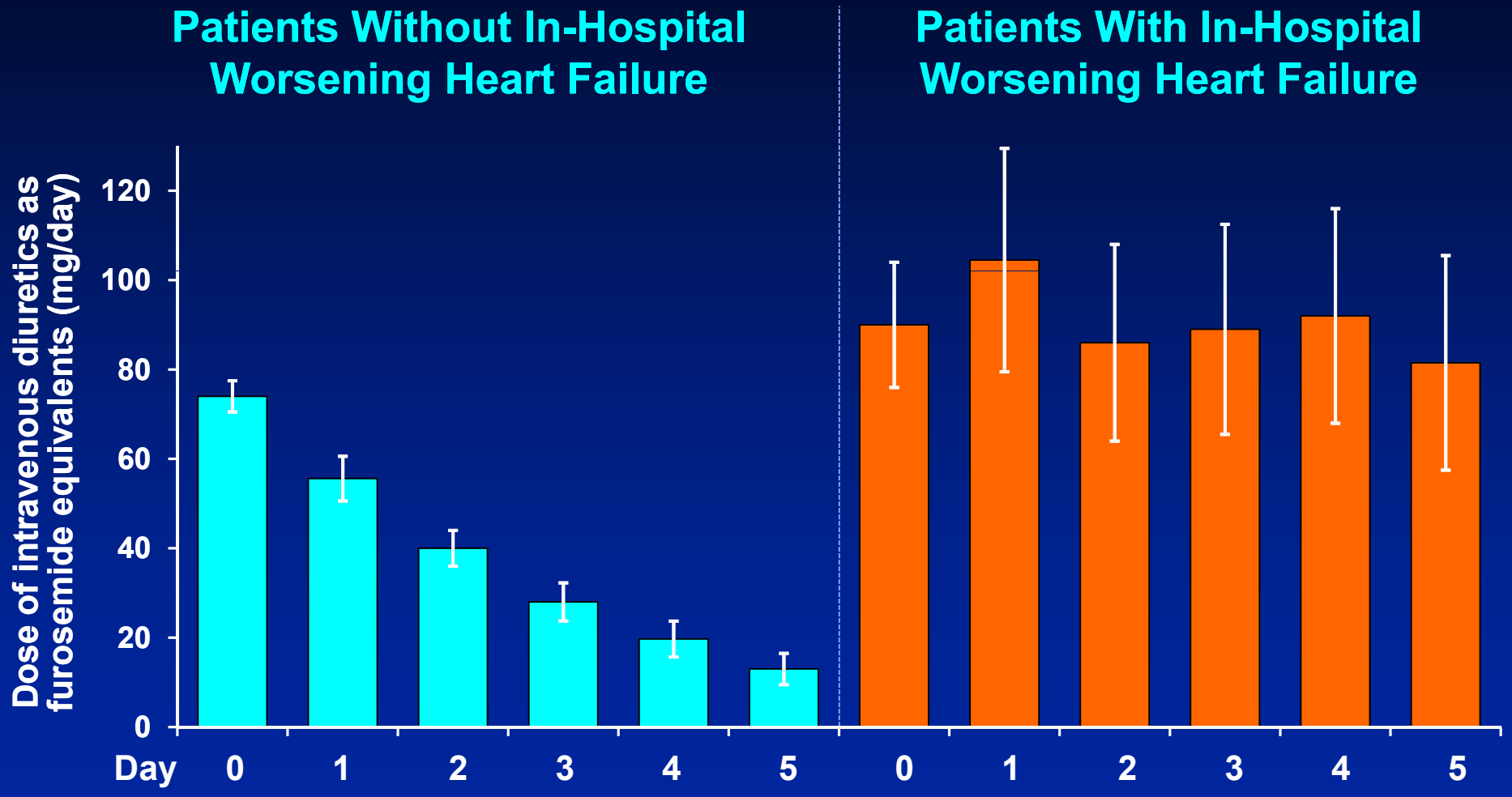
Robustness of Analyses of In-Hospital Worsening Heart Failure as a Clinical Event

- Was in-hospital worsening heart failure adequately documented as an event?
- **Was in-hospital worsening heart failure a clinically meaningful event?**
- Why was worst score assigned to in-hospital worsening heart failure from the time of its occurrence?
- Was worsening heart failure specified as an exploratory (and not primary) endpoint?
- Was the effect of serelaxin on in-hospital worsening heart failure robust?

Robustness of Analyses of In-Hospital Worsening Heart Failure as a Clinical Event

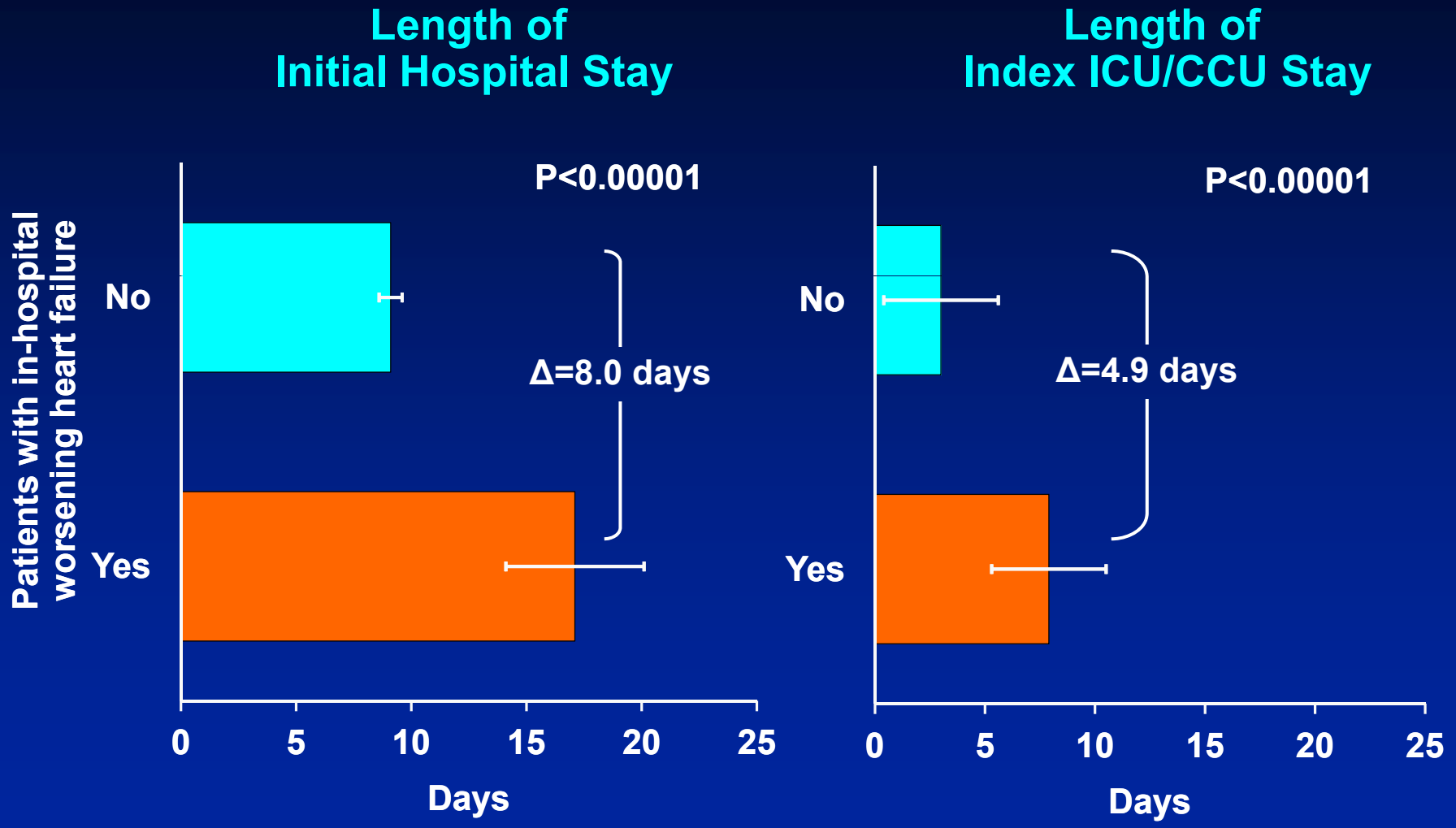
- Was in-hospital worsening heart failure adequately documented as an event?
- **Was in-hospital worsening heart failure a clinically meaningful event?**
  - **Meaningful deterioration in clinical status despite ongoing treatment, which requires immediate therapy with a rescue intervention**

Patients With Worsening Heart Failure Had Prolonged Use of Intravenous Diuretics



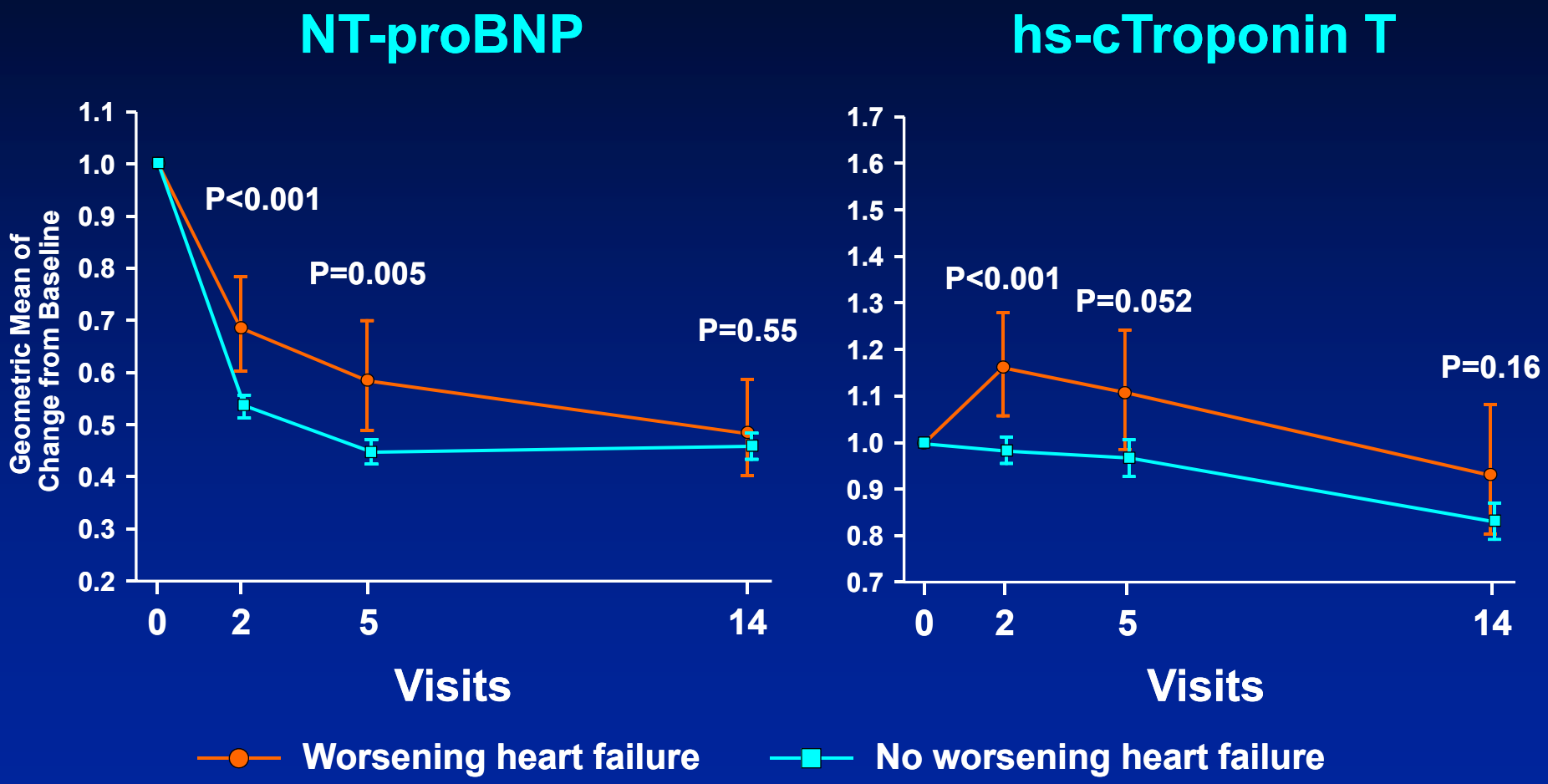
Patients without worsening heart failure (n=1037-1052) and with worsening heart failure (n=98-106)
Data presented as mean ± 95% CI

Patients With Worsening Heart Failure Had Prolonged Intensive Care and Hospital Stay



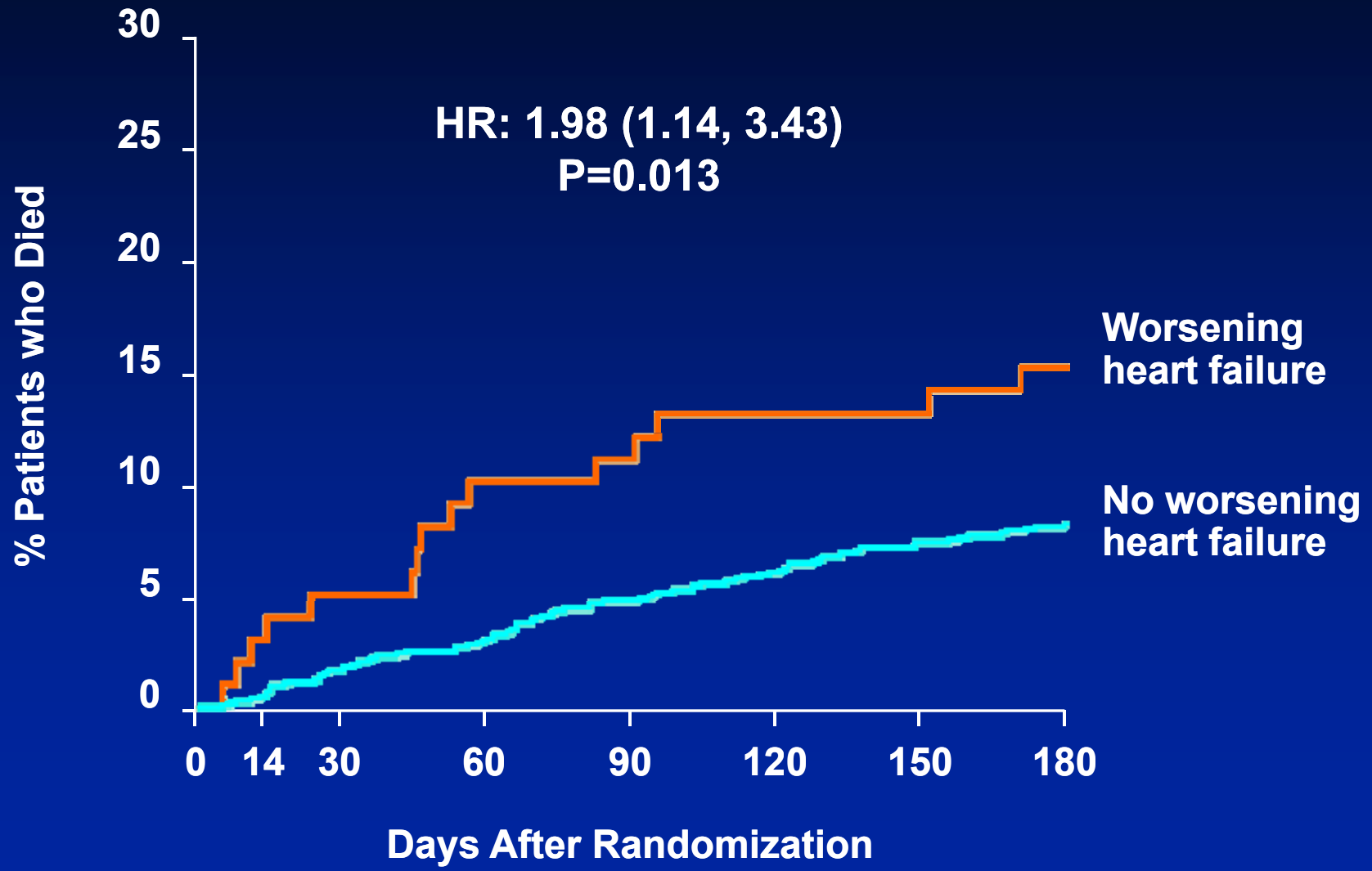
Patients with worsening heart failure (n=99) and without worsening heart failure (n=1055)
Excludes patients who died through Day 5. Data presented as mean ± 95% CI

Patients With Worsening Heart Failure Had Higher Levels of Cardiac Biomarkers



Shown are changes from baseline
P values refers to comparison of patients with and without worsening heart failure and are based on t-test

Patients With Worsening Heart Failure Had Increased Risk of All-Cause Death



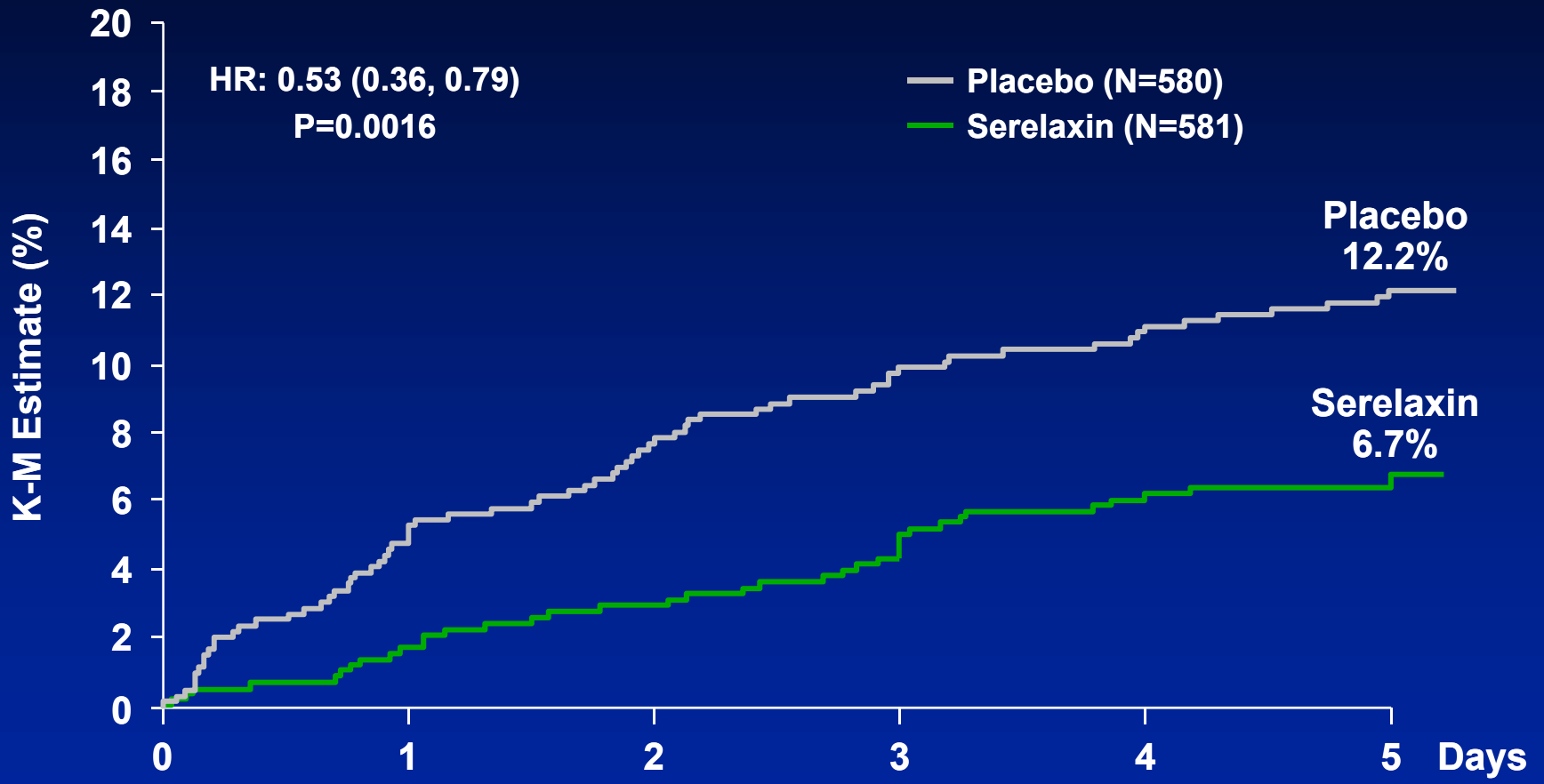
Robustness of Analyses of In-Hospital Worsening Heart Failure as a Clinical Event

- Was in-hospital worsening heart failure adequately documented as an event?
- Was in-hospital worsening heart failure a clinically meaningful event?
- **Why was worst score assigned to in-hospital worsening heart failure from the time of its occurrence?**
- Was worsening heart failure specified as an exploratory (and not primary) endpoint?
- Was the effect of serelaxin on in-hospital worsening heart failure robust?

Worst Score or Rank Assignment for Worsening Heart Failure

- Patients with in-hospital worsening heart failure represent a treatment failure
  - Require immediate rescue treatment
  - In the absence of rescue treatment, clinical status is unlikely to improve and is likely to worsen
- Clinical assessments following successful treatment will be meaningfully altered by the effects of rescue therapy
- Worst score or rank has been routinely assigned to patients who die or experience worsening heart failure in trials of acute heart failure

Time to Event Analysis of In-Hospital Worsening Heart Failure Through Day 5



Serelaxin	581	575	564	560	546	542
Placebo	580	567	544	527	519	513

HR ratio calculations are based on the less granular approach (day as time unit)

Robustness of Analyses of In-Hospital Worsening Heart Failure as a Clinical Event

- Was in-hospital worsening heart failure adequately documented as an event?
- Was in-hospital worsening heart failure a clinically meaningful event?
- Why was worst score assigned to in-hospital worsening heart failure from the time of its occurrence?
- **Was worsening heart failure specified as an exploratory (and not primary) endpoint?**
- Was the effect of serelaxin on in-hospital worsening heart failure robust?

Worsening Heart Failure as a Clinical Event Versus an Exploratory Endpoint

Event as Part of the Primary Endpoint

- Worsening heart failure or death through Day 5 were events that were components of the primary endpoint of Visual Analog Scale analyzed using worst observed score assignment

Exploratory Endpoint

- Worsening heart failure through Day 5 and Day 14 was an exploratory efficacy endpoint

Robustness of Analyses of In-Hospital Worsening Heart Failure as a Clinical Event

- Was in-hospital worsening heart failure adequately documented as an event?
- Was in-hospital worsening heart failure a clinically meaningful event?
- Why was worst score assigned to in-hospital worsening heart failure from the time of its occurrence?
- Was worsening heart failure specified as an exploratory (and not primary) endpoint?
- **Was the effect of serelaxin on in-hospital worsening heart failure robust?**

Serelaxin Reduced Both First and Recurrent Worsening Heart Failure Events Through Day 5

	Placebo (N=580)	Serelaxin (N=581)
First episode of worsening heart failure or death within 5 days	69 (11.9%)	37 (6.4%)
Recurrent worsening heart failure or death with prior event within 5 days	15 (2.6%)	4 (0.7%)
All worsening heart failure events and deaths within 5 days*	85	41

* Presented as numbers of events

Rescue Interventions Used to Respond to In-Hospital Worsening Heart Failure

	Placebo (N=580)	Serelaxin (N=581)
Number of patients who died or had in-hospital worsening or rehospitalization for HF through Day 5	69	37
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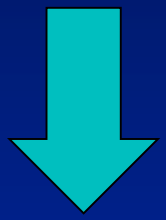
IV vasodilators (± IV diuretics)	13	8
IV diuretics only	38	19

One patient on placebo experienced HF rehospitalization at Day 4
3 patients died prior to Day 5 without preceding WHF in each treatment group

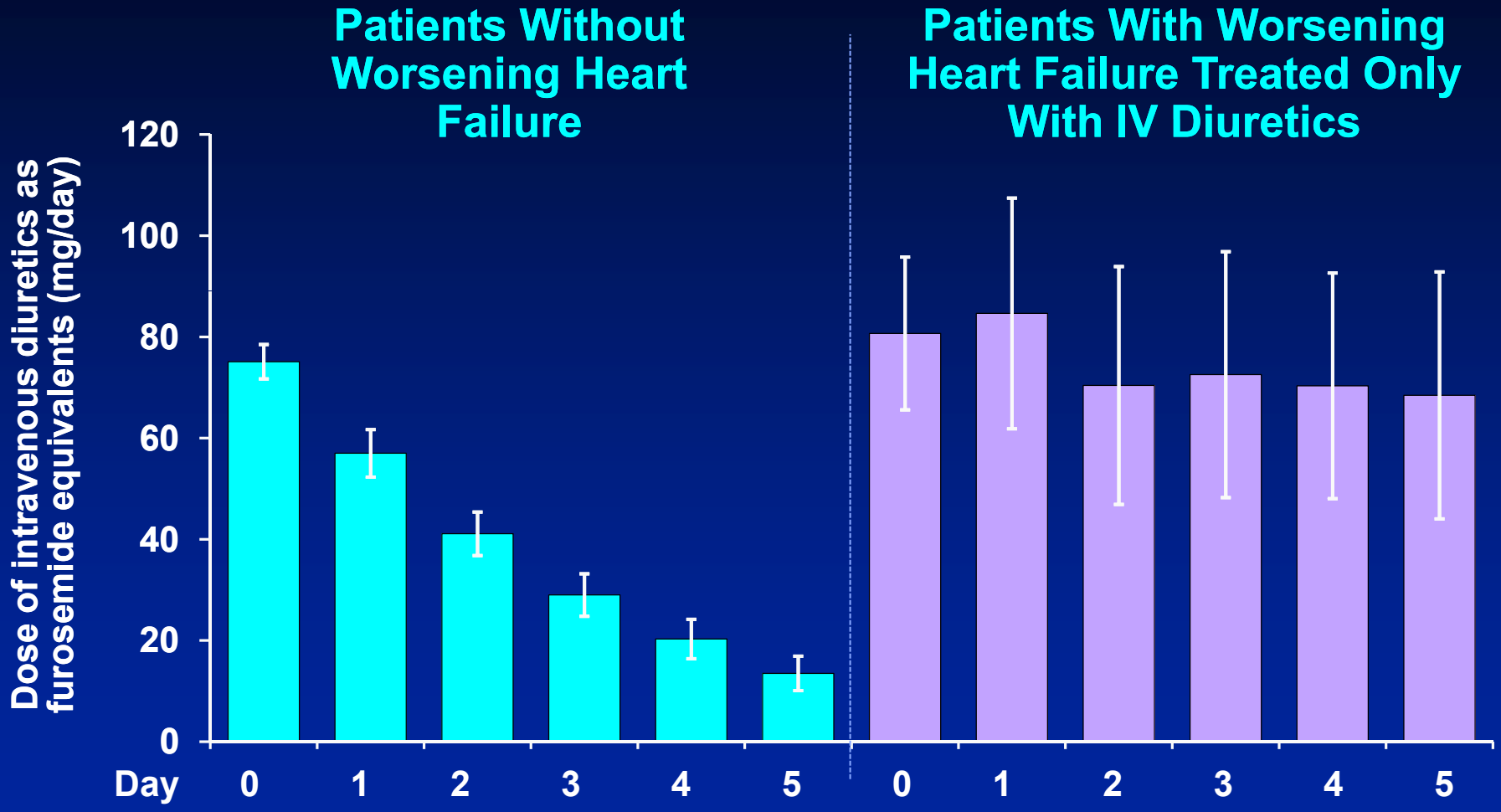
In-Hospital Worsening Heart Failure Is a Clinically Meaningful Event

Prolonged use of intravenous diuretics, leading to slow conversion to outpatient oral medications



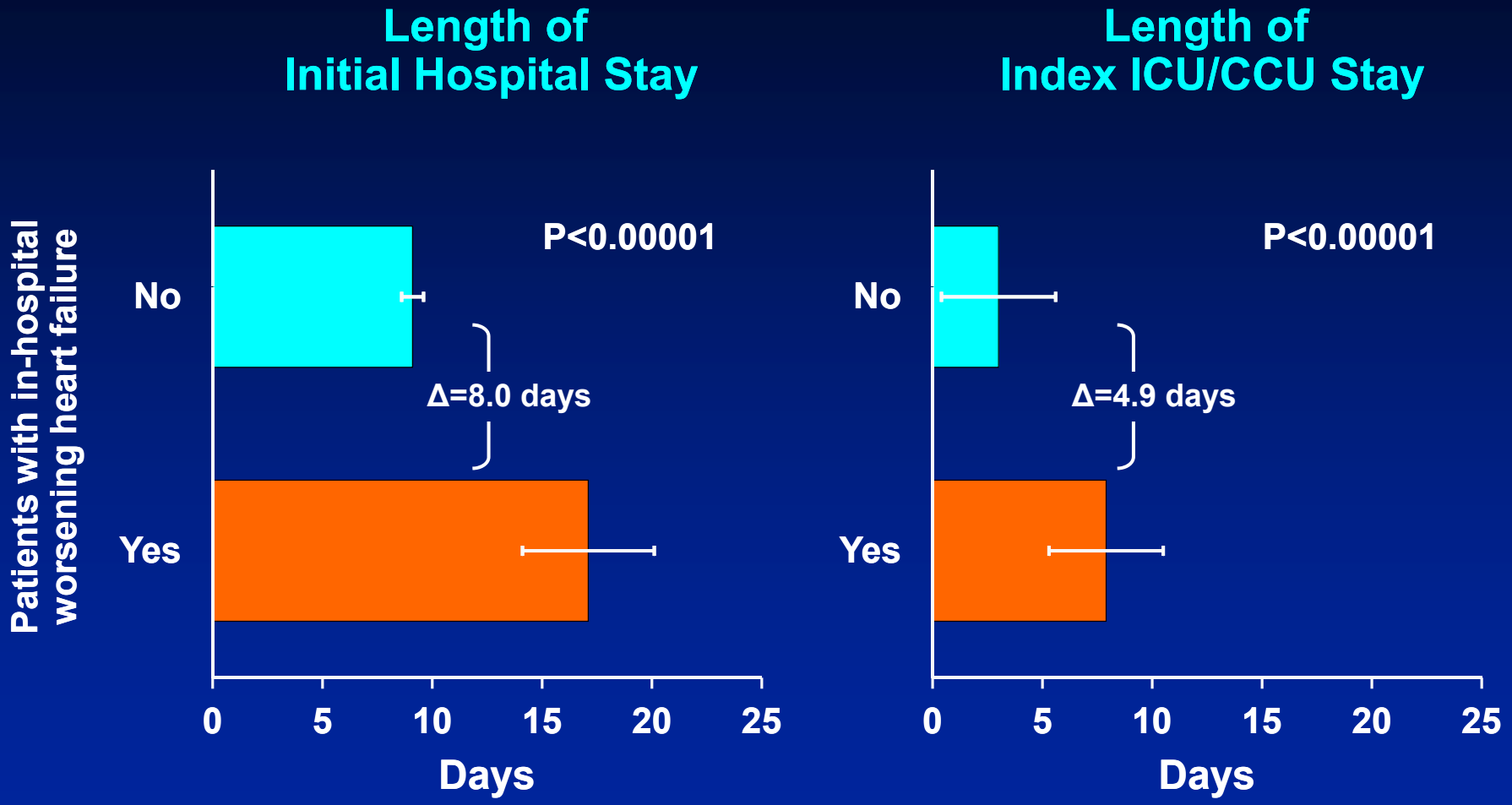
Prolonged duration of intensive care and index hospital stay

Patients With IV Diuretic Only Treated Events Had Prolonged Use of Intravenous Diuretics



Patients without worsening heart failure (n=1037-1052) and with worsening heart failure (n=58)
Data presented as mean ± 95% CI

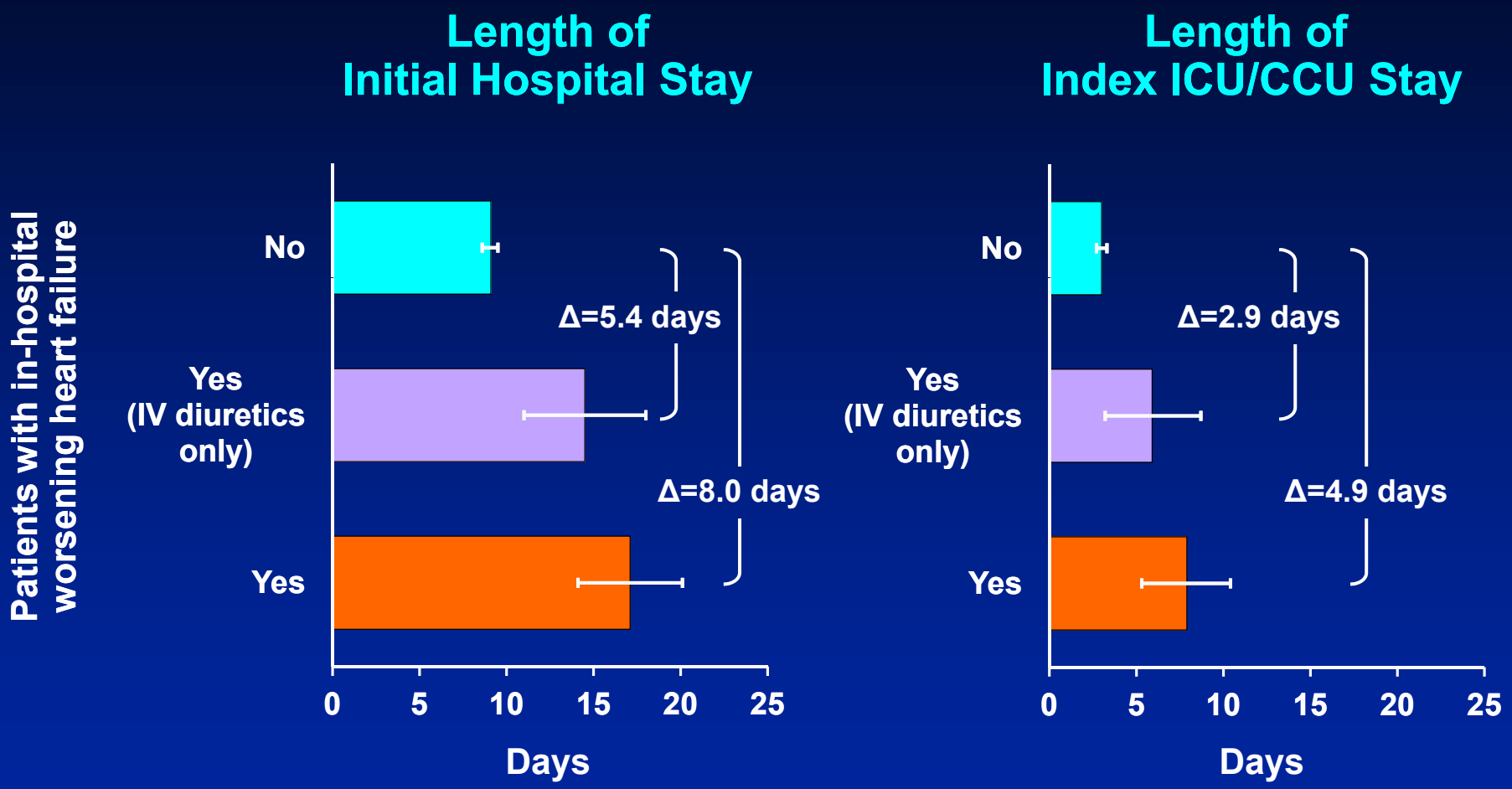
Patients With Worsening Heart Failure Had Prolonged Intensive Care and Hospital Stay



Patients with worsening heart failure treated only with IV diuretics (n=58), with any rescue treatment (n=99) and without worsening heart failure (n=1055). Excludes patients who died through Day 5

Data presented as mean ± 95% CI

Patients With IV Diuretic Only Treated Events Had Prolonged ICU and Hospital Stay



Patients with worsening heart failure treated only with IV diuretics (n=58), with any rescue treatment (n=99) and without worsening heart failure (n=1055). Excludes patients who died through Day 5

Data presented as mean ± 95% CI

Does Serelaxin Primarily Influence Mild Events Managed by Small Changes in Ongoing Therapy?

FDA Briefing Book:

"Treatments for WHF could be as simple as one extra dose of 20 mg of furosemide [or] an uptitration of nitroglycerine"

"Most cases of WHF and most of the difference between treatment groups were cases that could be ameliorated by increasing IV diuretics. There was a nominal difference between treatment groups in other therapies which include vasopressors, mechanical ventilation and circulatory support."

"Because most of the WHF cases were mild enough to be treated with increased IV diuretic use alone the main difference between the groups was a difference in relatively mild WHF treatable with increased diuretic use."

Pages 69-70

Did Serelaxin Primarily Prevent Mild Worsening Events Treated With IV Diuretics Only?

WHF events through Day 5

Rescue Intervention, n	Severity of AEs	Placebo	Serelaxin
IV inotropes, mechanical or circulatory support	Mild	1	0
	Moderate	10	1
	Severe	6	5
IV nitrates with or without IV diuretics	Mild	5	1
	Moderate	7	6
	Severe	5	2
IV diuretics only	Mild	13	6
	Moderate	25	15
	Severe	3	1

Patients who died or were rehospitalized without prior WHF events excluded

Worsening Heart Failure Events With More Intensive Rescue Intervention

	Placebo (N=580)	Serelaxin (N=581)
Patients who died or who experienced WHF leading to rehospitalization within 5 days		
Patients with WHF within 5 days treated with IV positive inotropic drug or mechanical intervention		
Patients with WHF within 5 days treated with new IV nitrates or IV nitroprusside		
Patients with WHF within 5 days treated with reinitiation or doubling of daily dose of IV diuretic		

Worsening Heart Failure Events With More Intensive Rescue Intervention

	Placebo (N=580)	Serelaxin (N=581)
Patients with WHF event included in the analysis of the 5-day primary endpoint	69	37
Patients who died or who experienced WHF leading to rehospitalization within 5 days	5	4
Patients with WHF within 5 days treated with IV positive inotropic drug or mechanical intervention	17	6
Patients with WHF within 5 days treated with new IV nitrates or IV nitroprusside	13	7
Patients with WHF within 5 days treated with reinitiation or doubling of daily dose of IV diuretic	14	7
Total	49	24

P=0.003

Do Sensitivity Analyses Confirm the Effect of Serelaxin on the Primary Endpoint?

FDA Briefing Book:

"... Sensitivity analyses demonstrate that the results of the trial are dependent on the imputation scheme used for when a patient had WHF. It is notable that only the prespecified imputation scheme which treats all degrees of severity of WHF equally keeps the P value below the prespecified 0.025 mark needed for success..."

Sensitivity Analyses: Hierarchical Ranking of VAS AUC Components by Clinical Course

Death:

- Earliest death ranked worst

WHF:

- Ranked better than death, with subranks based on type of event

Alive, no WHF:

- Positive VAS scores ranked better

Finkelstein & Schoenfeld Approach, 1999

Primary Endpoint Analyses Based on Clinically Ranked Outcomes Without Use of Arbitrary Numerical Score Assignment

	P value
Analysis of clinically ranked outcomes	
All worsening heart failure events assigned same rank	0.0190
Earlier worsening heart failure events assigned worse rank than later events*	0.0110
Recurrent worsening events assigned worse rank than single events	0.0150
Aggressive interventions ranked worse than IV vasodilators, ranked worse than IV diuretics	0.0183
Prespecified primary efficacy analysis	**0.0075**

* In Novartis Briefing Book, other sensitivity analysis presented in addendum

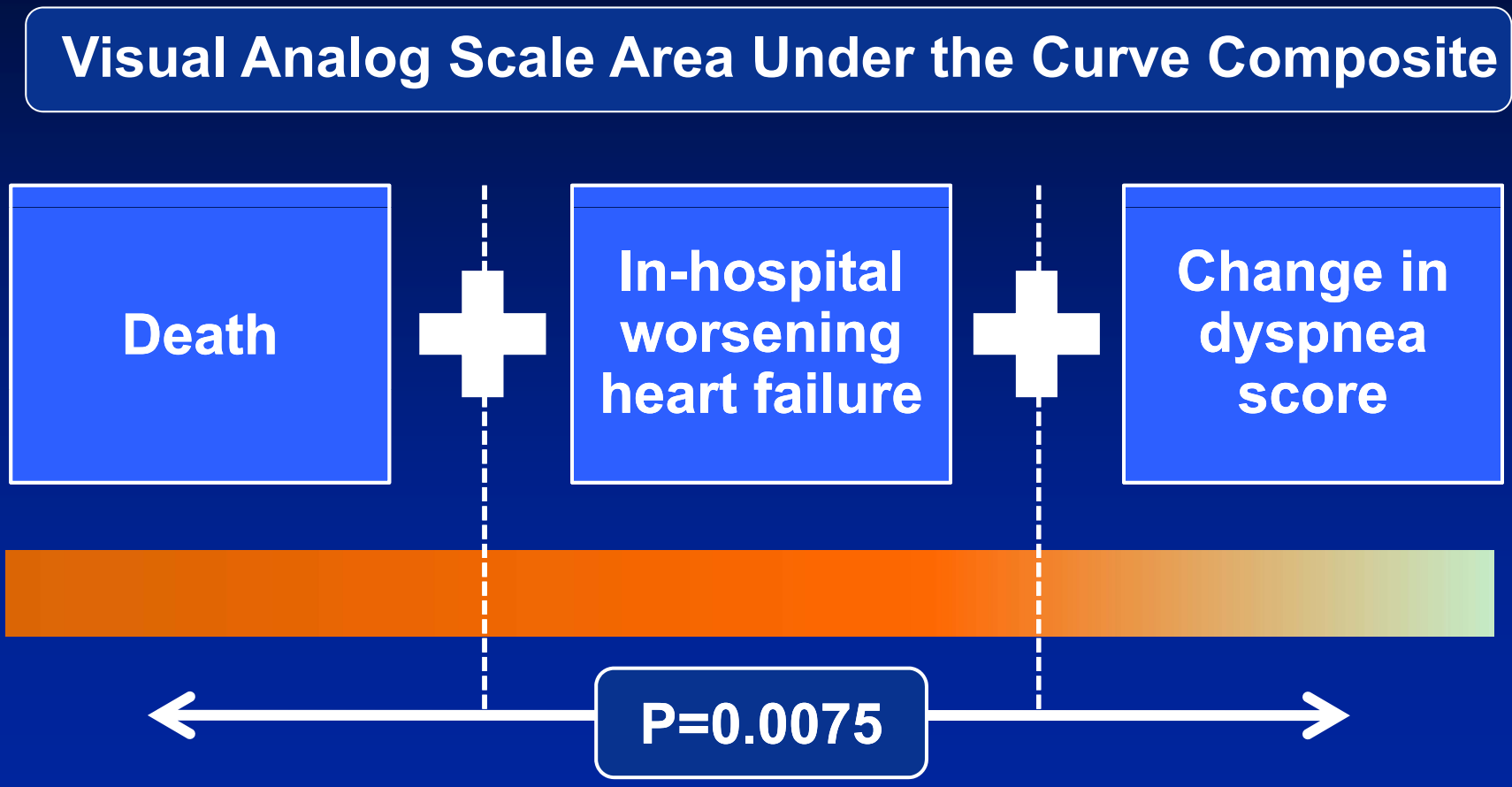
Observed VAS scores and log rank test used

Follows ideas of Finkelstein & Schoenfeld (1999) and Felker (2010)

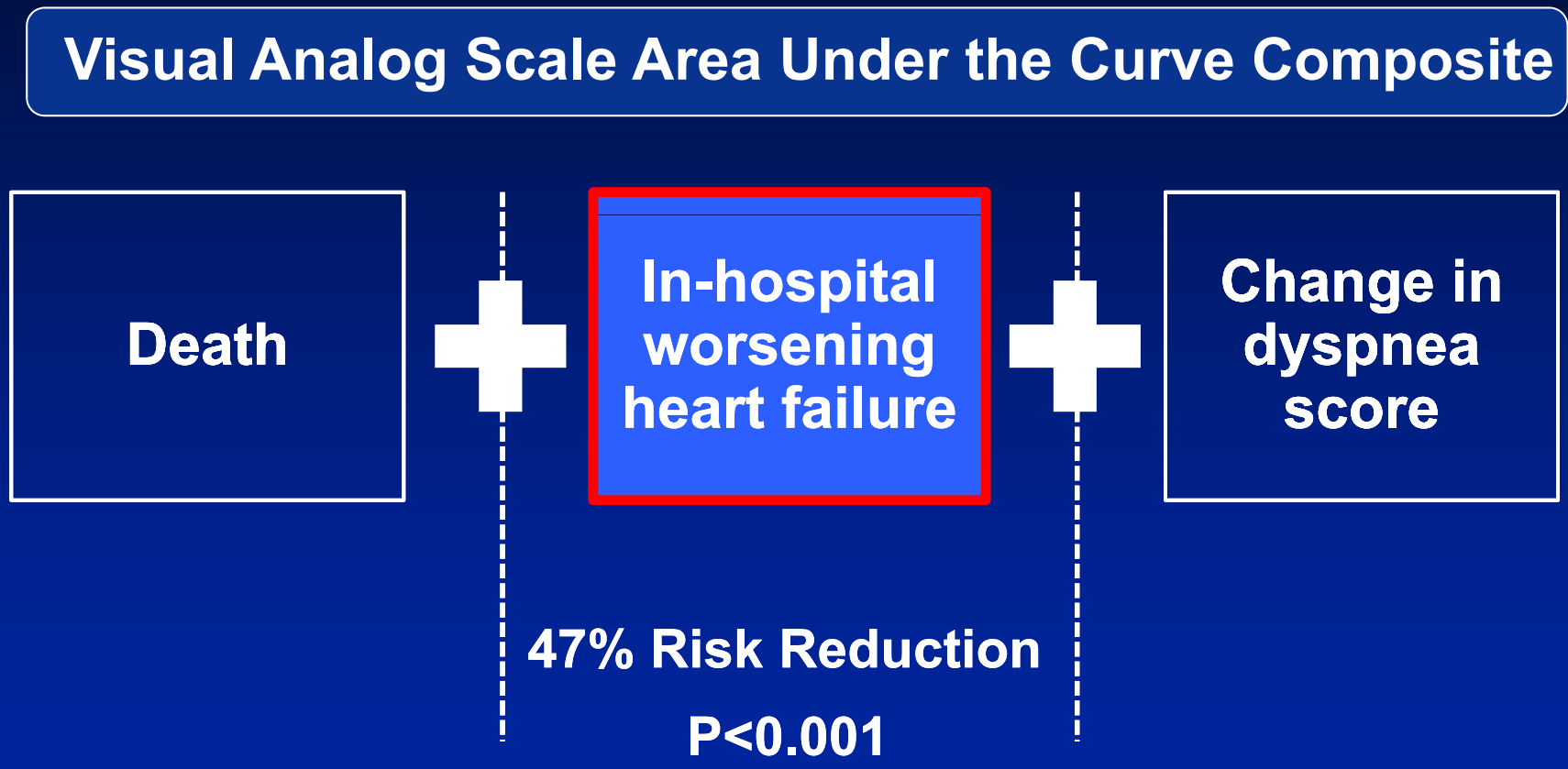
Analysis of In-Hospital Worsening Heart Failure as a Clinical Event

- Worsening heart failure was a prespecified component of the primary endpoint and drove the treatment difference
- Worsening heart failure was a fully documented event
- Worsening heart failure regardless of rescue therapy led to prolonged use of IV medications and longer ICU and hospital stays for the index event
- Serelaxin reduced the risk of first and recurrent events
- Serelaxin reduced the risk of treatment failures regardless of severity including worsening events treated with more intensive rescue interventions
- Analyses of clinically ranked outcomes without numerical assignment confirmed primary endpoint result

RELAX-AHF Trial Met Its Primary Endpoint



RELAX-AHF Trial Met Its Primary Endpoint Through a Reduction in Worsening Events



Additional Efficacy and Safety Results

Thomas Severin, MD, FESC

Global Program Medical Director, Critical Care
Novartis Pharma AG

Overview of Presentation

- RELAX-AHF Trial
  - Secondary endpoints
  - Other efficacy endpoints
  - Evaluation of safety
  - Cardiovascular and all-cause mortality
- Pre-RELAX-AHF Trial
- Benefit-to-Risk

Overview of Presentation

- RELAX-AHF Trial
  - Secondary endpoints
    - Days alive and out of hospital through Day 60
    - Cardiovascular death or rehospitalization for heart failure or renal failure through Day 60
  - Other efficacy endpoints
  - Evaluation of safety
  - Cardiovascular and all-cause mortality
- Pre-RELAX-AHF Trial
- Benefit-to-Risk

Days Alive and Out of Hospital Through Day 60

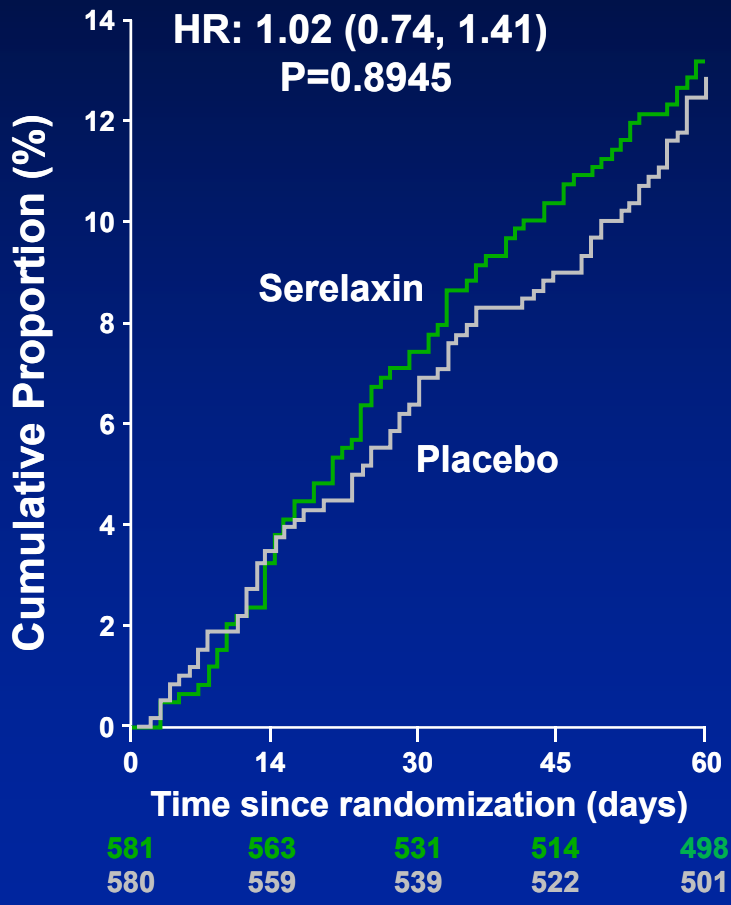
	Placebo (N=580)	Serelaxin (N=581)
Mean (95% CI)	47.7 (46.7, 48.7)	48.3 (47.3, 49.2)
Median (25, 75% IQR)	52 (45.0, 55.0)	52 (46.0, 55.0)
P value		0.3682

Days alive out of hospital = total follow-up time (60 days) minus number of days spent in hospital or since death

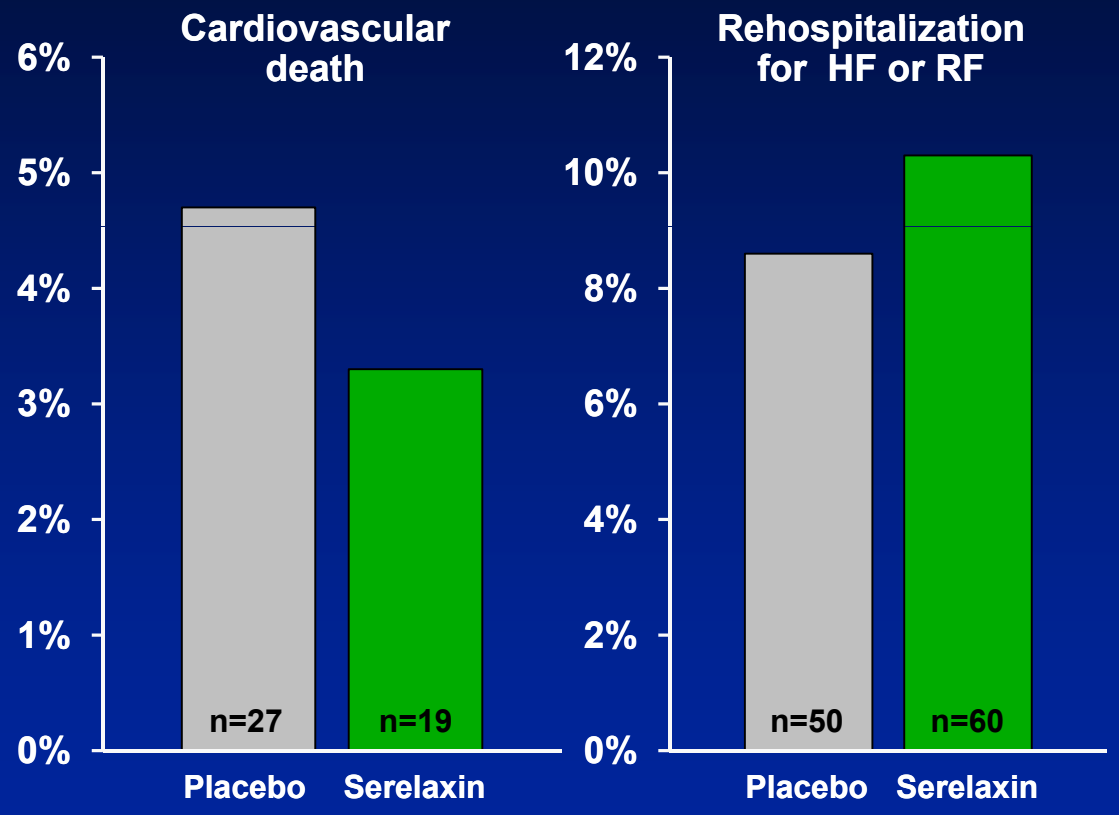
P value by 2-sided Wilcoxon rank sum test

Cardiovascular Death or Rehospitalization for Heart Failure or Renal Failure Through Day 60

Time to First Event

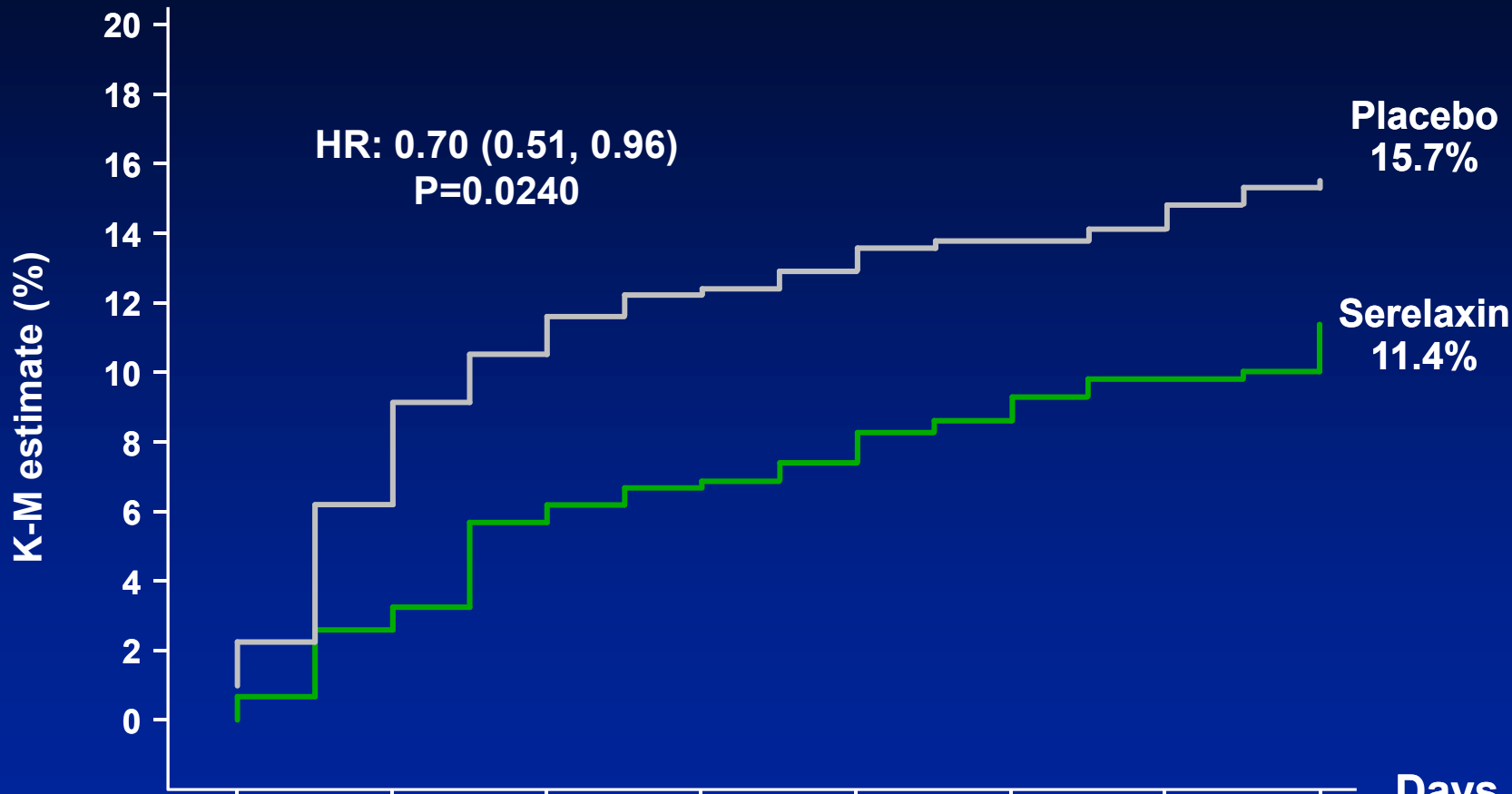


Endpoint Components



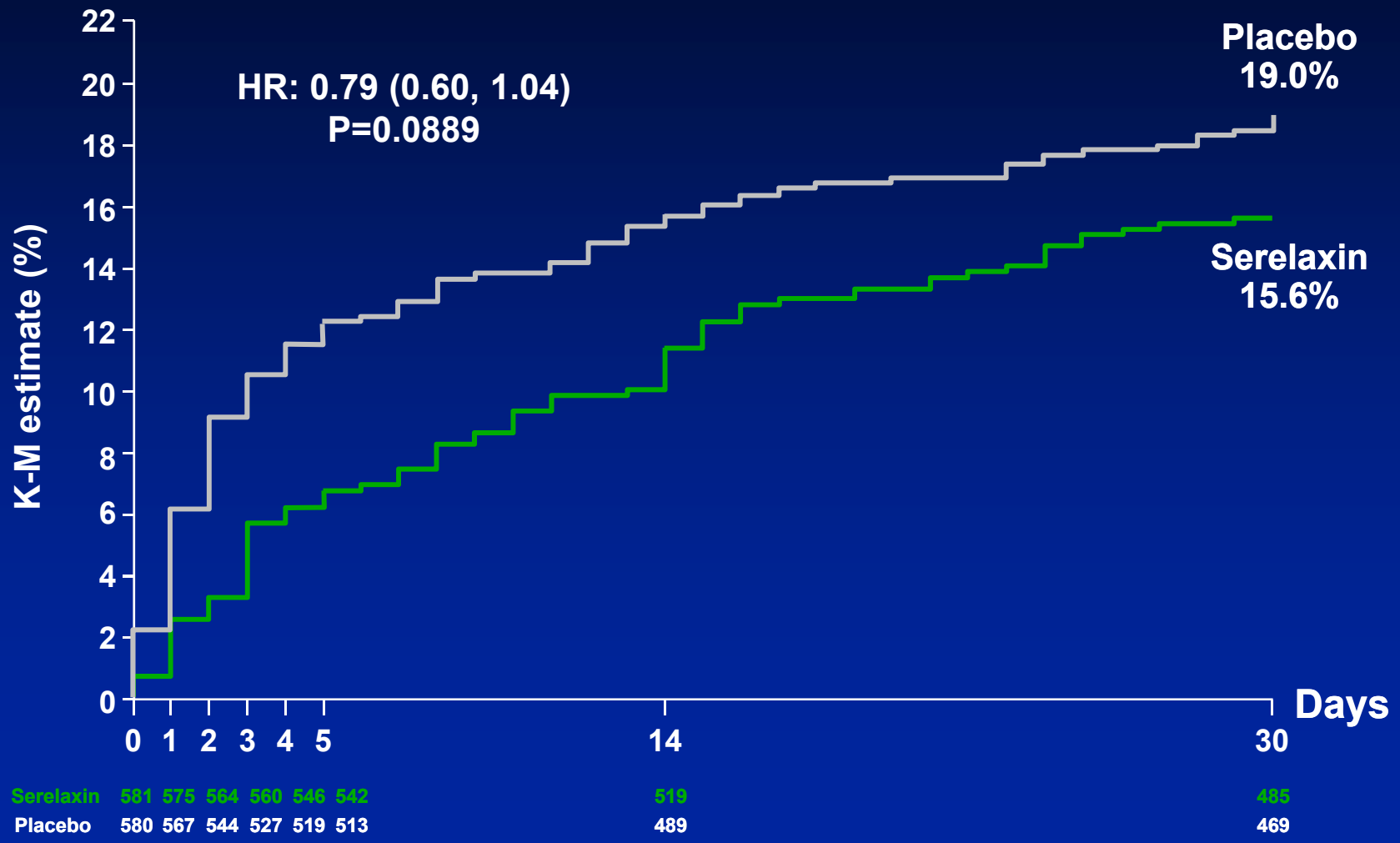
P value by log rank test, HR estimate by Cox model

All-Cause Death, Worsening Heart Failure or Rehospitalization for Heart Failure Through Day 14



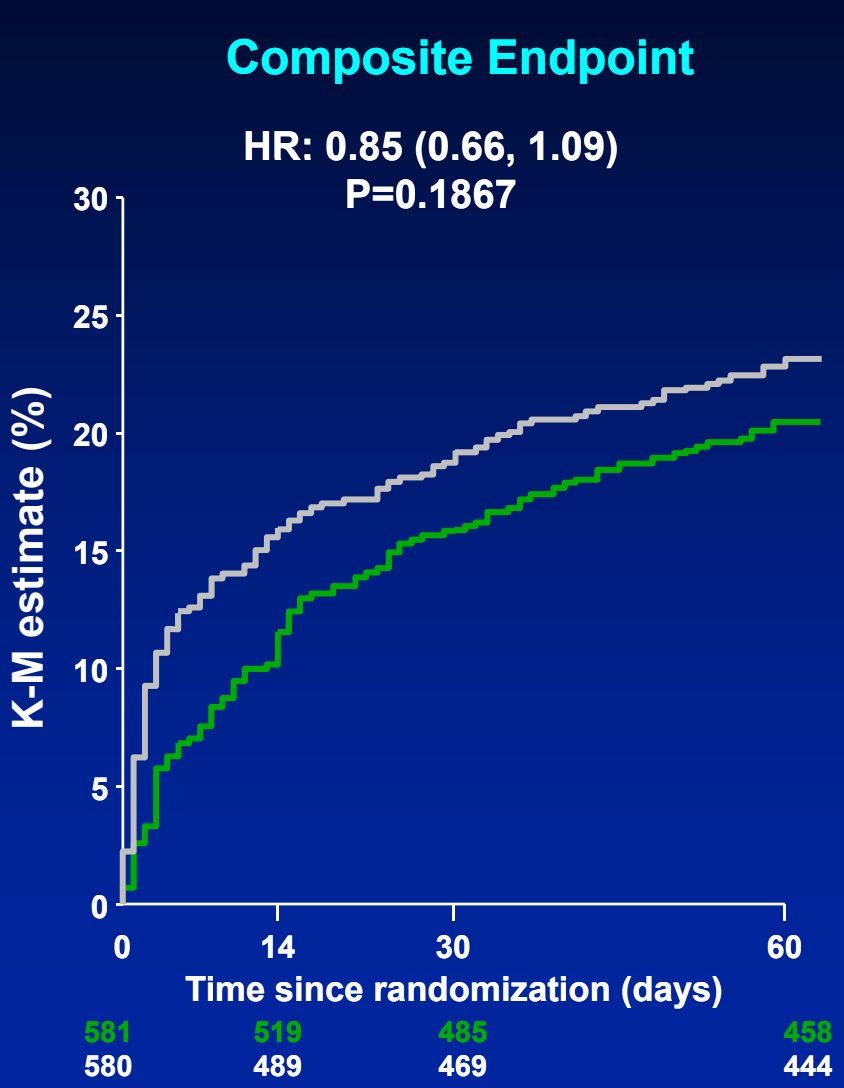
The hazard ratio, CI and P value based on a Cox regression model with treatment as a factor

All-Cause Death, Worsening Heart Failure or Rehospitalization for Heart Failure Through Day 30

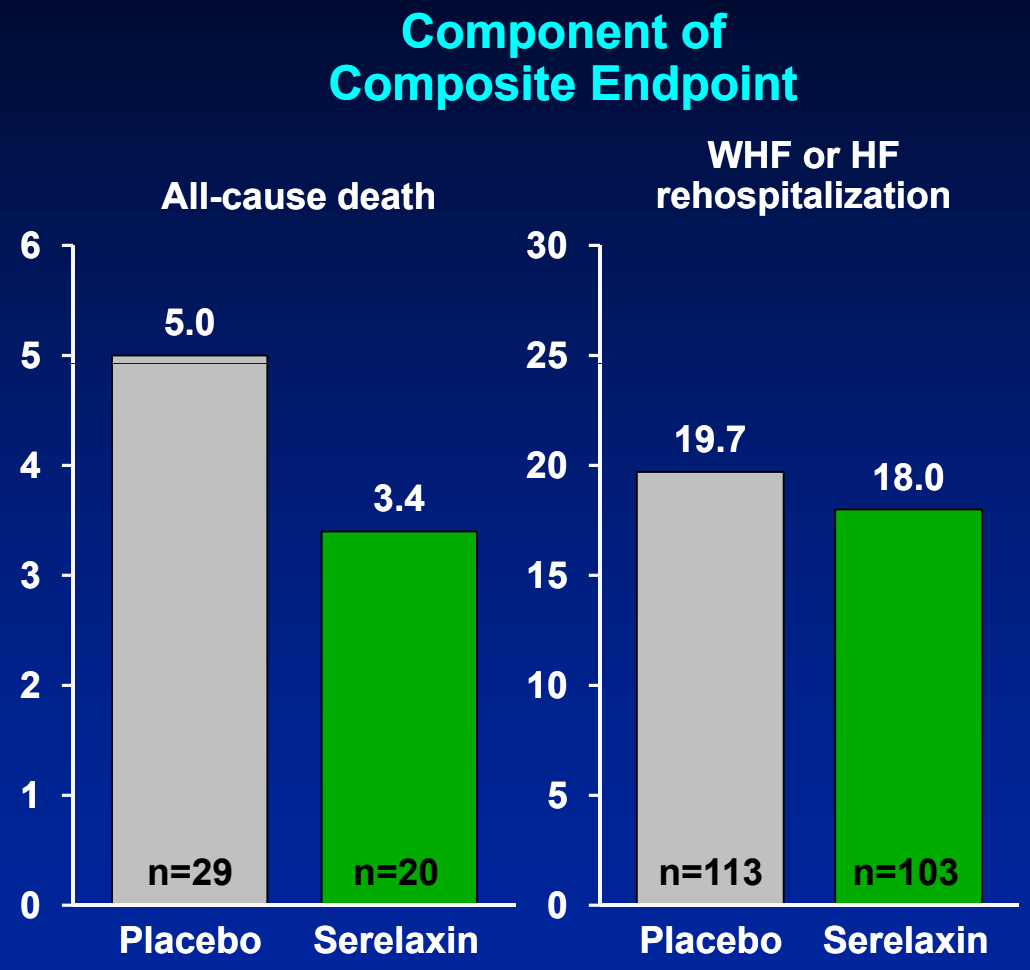


The hazard ratio, CI and P value based on a Cox regression model with treatment as a factor

Composite of All-Cause Death, Worsening Heart Failure or HF Rehospitalization through Day 60



P value based on log rank test

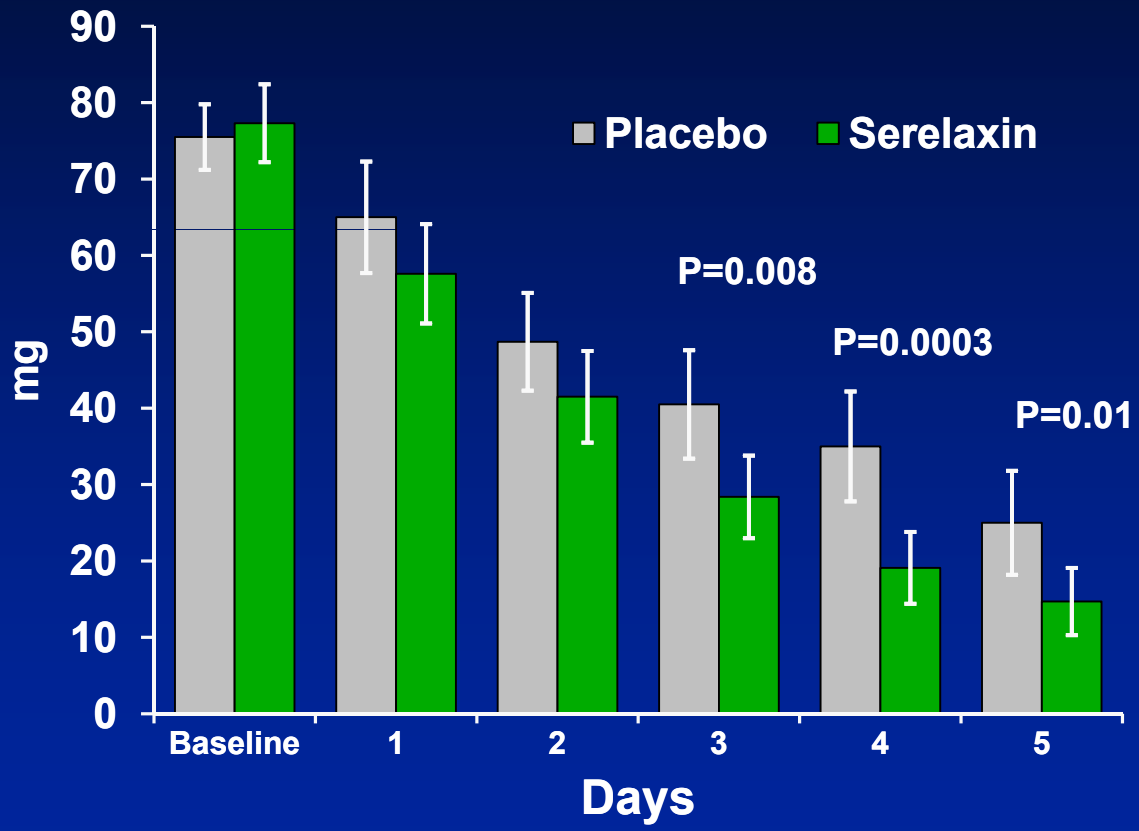


Overview of Presentation

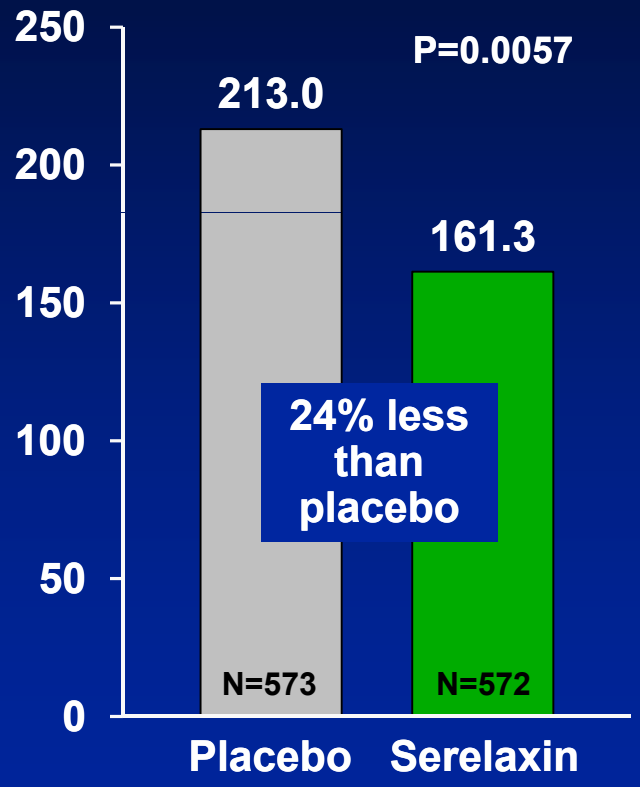
- RELAX-AHF Trial
  - Secondary endpoints
  - Other efficacy endpoints
    - Use of intravenous diuretics
    - Length of index hospital stay
    - Cardiac and renal biomarkers
  - Evaluation of safety
  - Cardiovascular and all-cause mortality
- Pre-RELAX-AHF Trial
- Benefit-to-Risk

Use of Intravenous Diuretics Through Day 5

Daily Dose of Intravenous Diuretics During First 5 Days



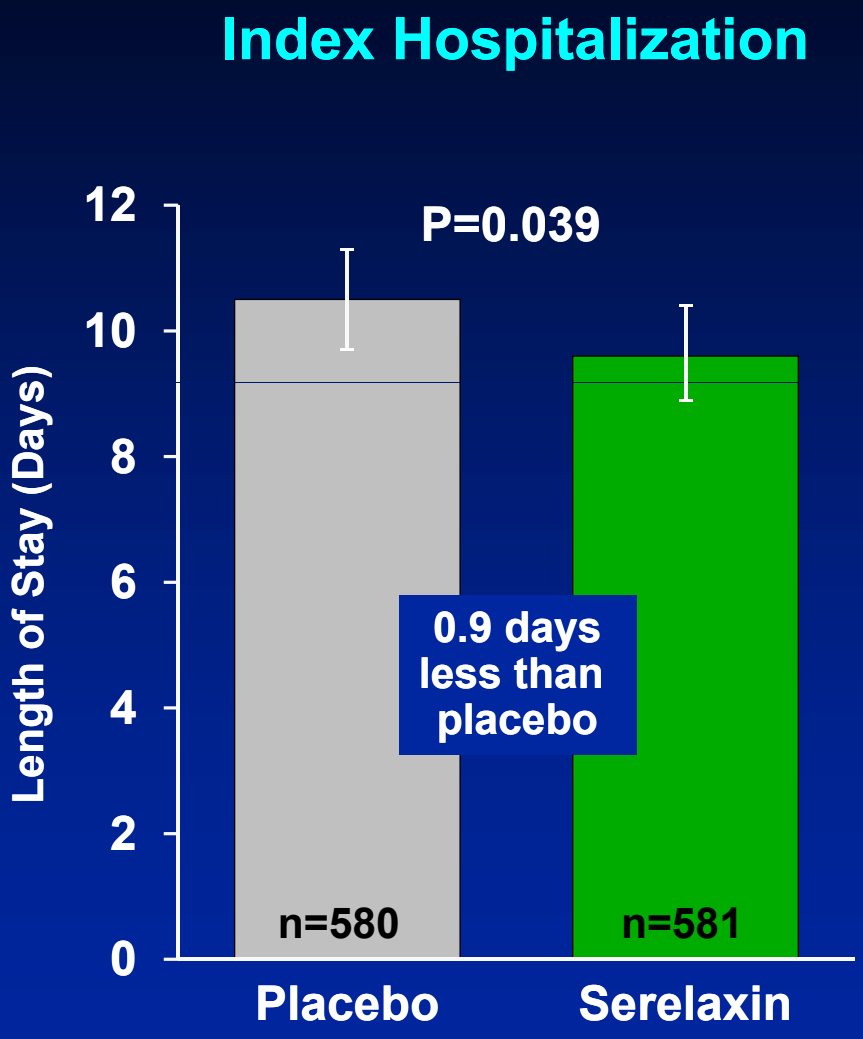
Cumulative Dose of IV Diuretics Through Day 5

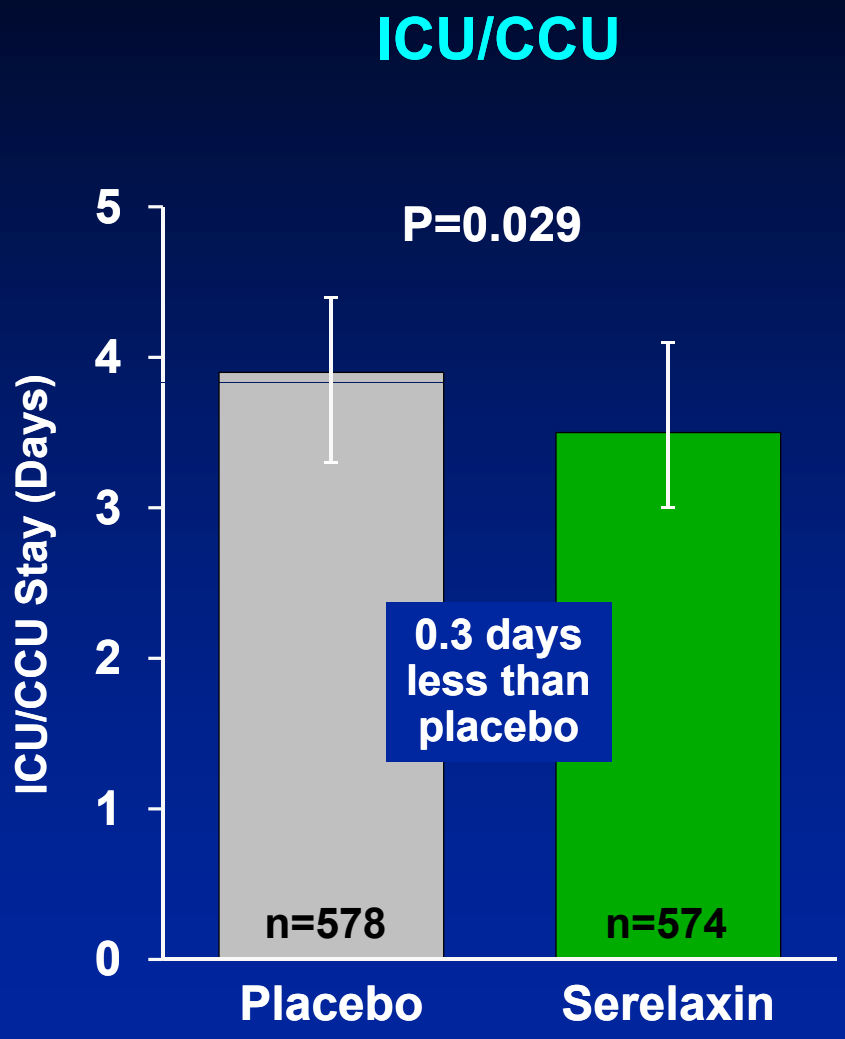


P value based on t-test; Data presented as mean ± 95% CI

Calculation of furosemide equivalent doses (mg) for torsemide, bumetanide and ethacrynic acid are actual dose (mg) multiplied by a constant (2, 20 or 0.8, respectively)

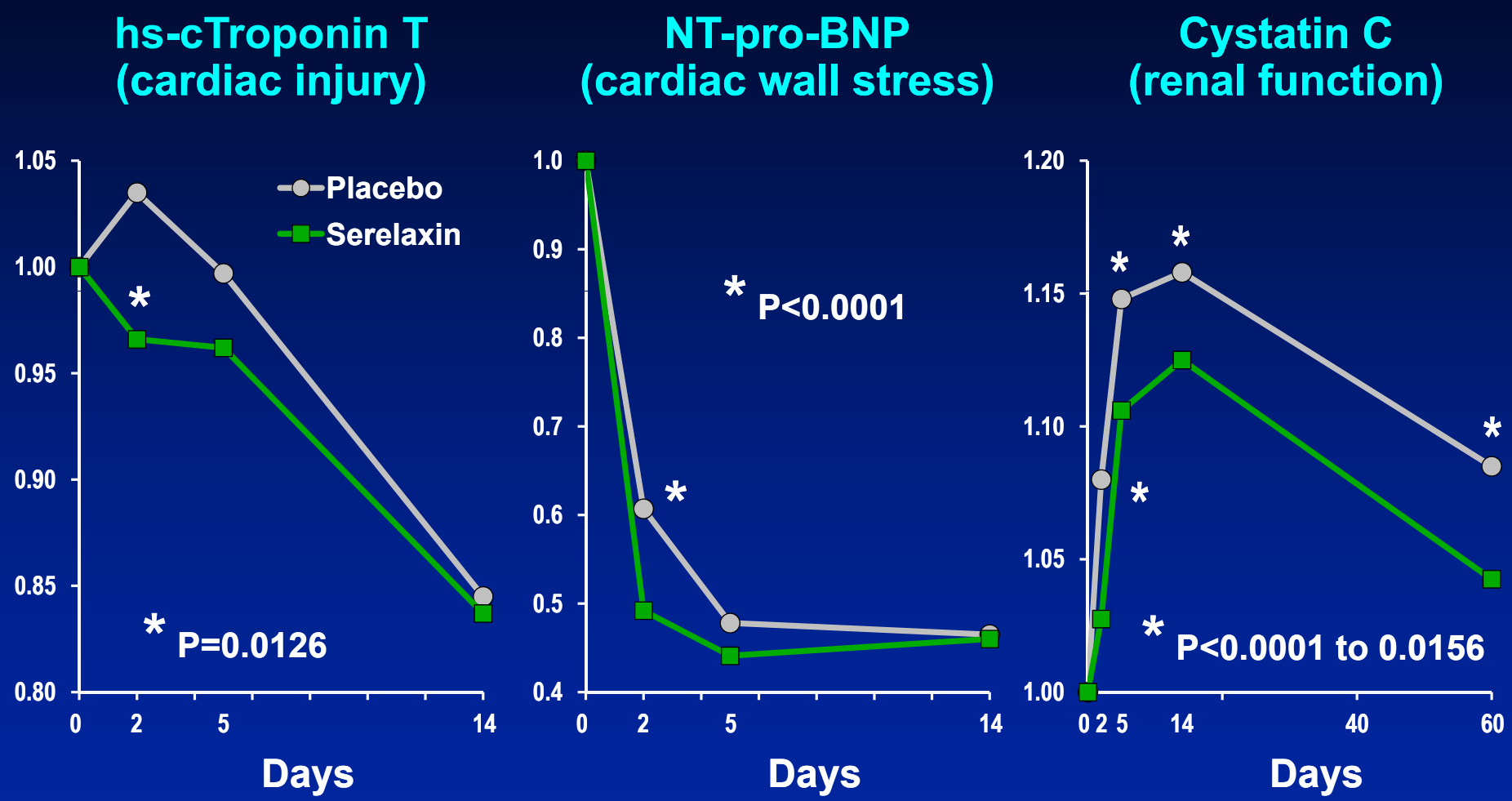
Length of Stay in Hospital and ICU/CCU





P value by Wilcoxon rank sum test (death assigned longest length of stay plus 1 day)

Cardiac and Renal Biomarkers

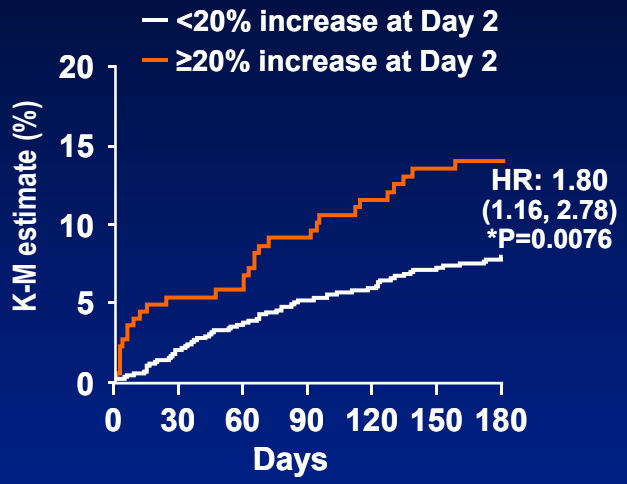


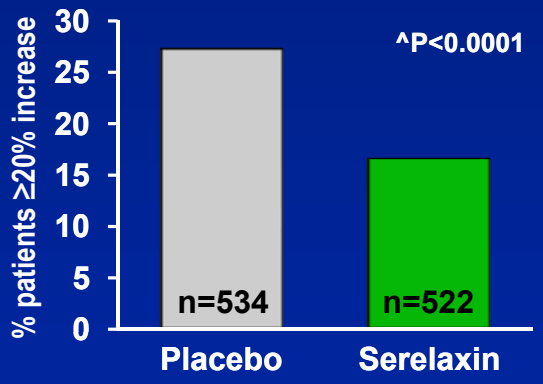
All values represent geometric mean changes; no worst score assignment was used

Metra M et al., J Am Coll Cardiol 2013, 61(2):196-206

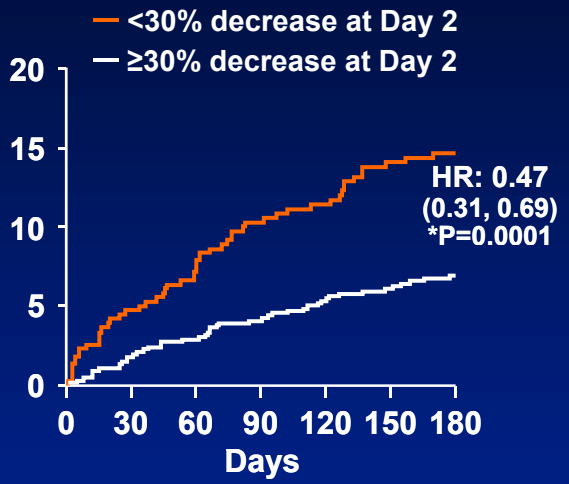
Cardiac and Renal Biomarker Associations with All-Cause Mortality

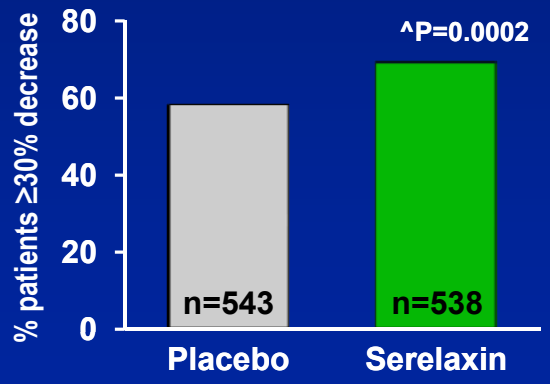
hs-cTroponin T



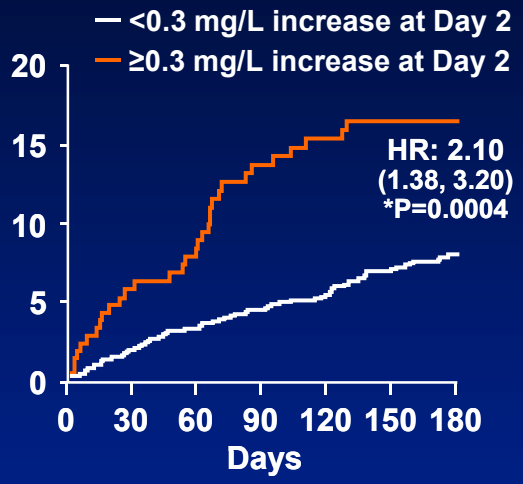


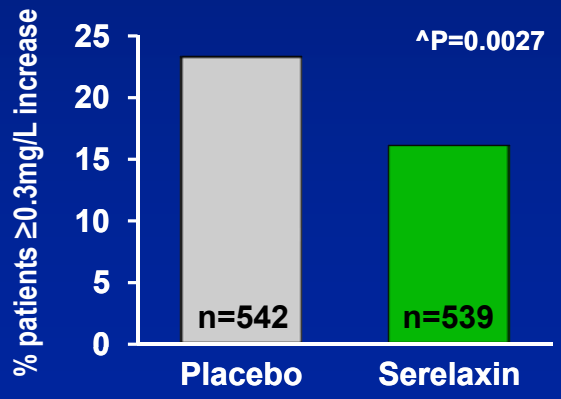
NT-pro-BNP





Cystatin-C





HR and 95% CI based on Cox regression models

*P value based on log rank test; ^P value based on the Wald statistic from the logistic regression model

RELAX-AHF: Consistent Pattern of Benefit Across Multiple Clinical Endpoints

- Lower risk of in-hospital worsening heart failure
  - Improved scores on Visual Analog Scale
  - Better response for signs and symptoms
- Less use and more rapid taper of IV diuretics
- Shorter index hospital stay
- Favorable effect on cardiac and renal biomarkers reflecting injury or function
- Neutral effects on Day 60 endpoints

Overview of Presentation

- RELAX-AHF Trial
  - Secondary endpoints
  - Other efficacy endpoints
  - Evaluation of safety
    - Blood pressure events
    - Cardiac failure adverse events
    - Renal impairment adverse events
  - Cardiovascular and all-cause mortality
- Pre-RELAX-AHF Trial
- Benefit-to-Risk

Reports of Adverse Events and Serious Adverse Events

	Placebo (N=570)	Serelaxin (N=568)
Subjects with any adverse event (AE), n (%)	320 (56.1)	305 (53.7)
Subjects with any drug-related AE	46 (8.1)	47 (8.3)
Subjects with any AE leading to study drug discontinuation	22 (3.9)	26 (4.6)
Subjects with any serious adverse event (SAE)	78 (13.7)	86 (15.1)
Subjects with any drug-related SAEs	2 (0.4)	3 (0.5)
Subjects with any SAE leading to drug discontinuation	3 (0.5)	5 (0.9)
Serious AE with an outcome of death*	15 (2.6)	10 (1.8)

Reports of non-serious adverse events were collected to Day 5
Reports of serious adverse events were collected to Day 14

* Data presented includes patients with SAEs before Day 14 who died after Day 14

Confirmed Blood Pressure Decrease Events

	Placebo (N=570)	Serelaxin (N=568)
Patients with a confirmed BP decrease event, n (%)	103 (18.1)	167 (29.4)
Median time to first confirmed BP decrease event, hr	17.9	10.0
Investigator response to BP decrease event, n		
50% dose reduction but remained on study drug	31	59
50% dose reduction with subsequent discontinuation	12	16
Immediate discontinuation of study drug	59	91

Confirmed BP decrease event defined as decrease in systolic BP by > 40 mmHg and/or to < 100 mmHg at any time during infusion

Adverse Events – Cardiac Failure to Day 14

	Placebo (N=570)	Serelaxin (N=568)
SMQ Cardiac failure, n (%)	66 (11.6)	49 (8.6)
Cardiac failure congestive	35 (6.1)	24 (4.2)
Cardiac failure	11 (1.9)	8 (1.4)
Cardiac failure acute	6 (1.1)	6 (1.1)
Acute pulmonary edema	3 (0.5)	4 (0.7)
Acute left ventricular failure	0 (0.0)	2 (0.4)
Cardiac asthma	0 (0.0)	1 (0.2)
Cardiogenic shock	1 (0.2)	1 (0.2)
Ejection fraction decreased	1 (0.2)	1 (0.2)
Pulmonary edema	2 (0.4)	1 (0.2)
Edema peripheral	4 (0.7)	1 (0.2)
Hepatic congestion	3 (0.5)	0 (0.0)
Cardiac resynchronization therapy	1 (0.2)	0 (0.0)
Cardiorenal syndrome	1 (0.2)	0 (0.0)
Left ventricular failure	1 (0.2)	0 (0.0)
Pulmonary congestion	1 (0.2)	0 (0.0)

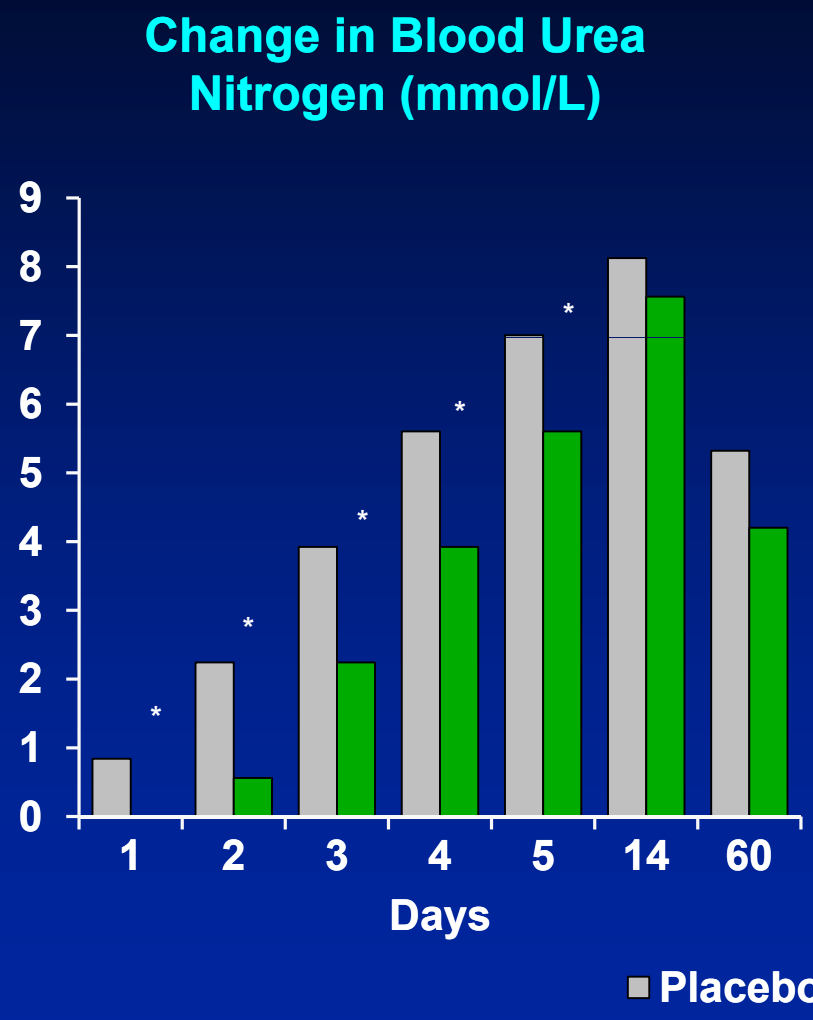
SMQ = Standardized MedDRA Query

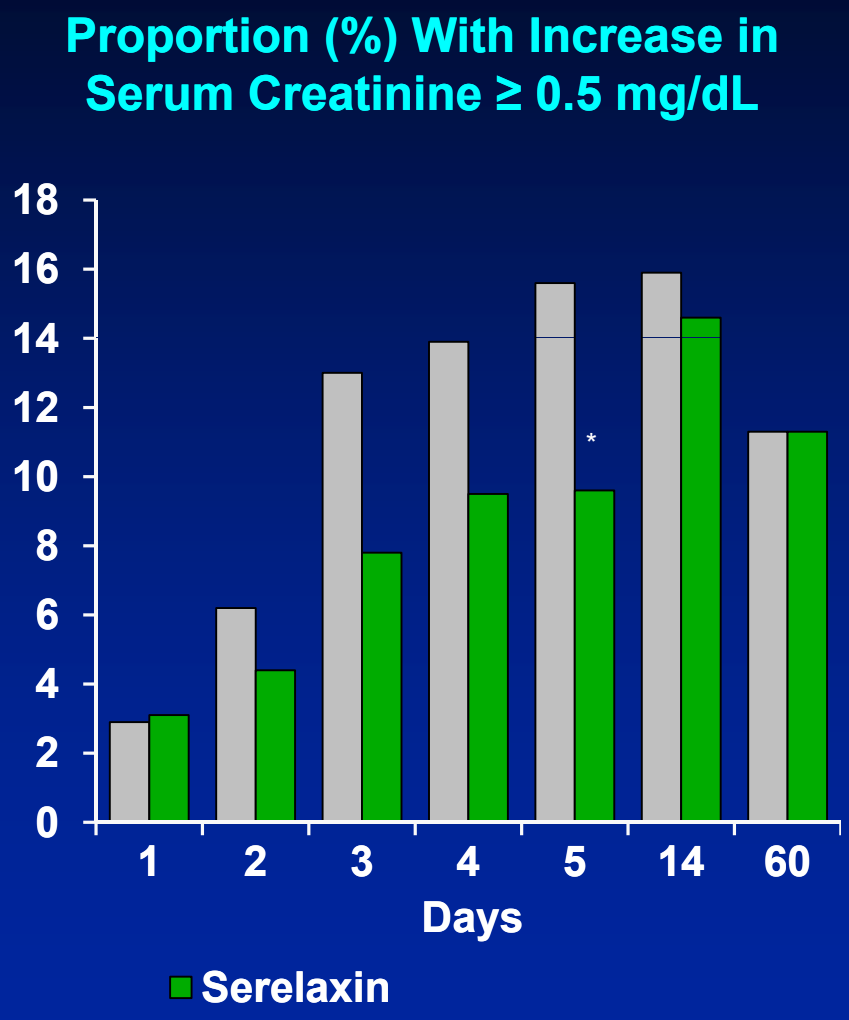
Adverse Events – Renal Impairment to Day 14

	Placebo (N=570)	Serelaxin (N=568)
SMQ Acute Renal Failure, n (%)	51 (8.9)	32 (5.6)
Renal failure	25 (4.4)	14 (2.5)
Blood creatinine increased	23 (4.0)	14 (2.5)
Renal failure acute	0	2 (0.4)
Azotemia	1 (0.2)	1 (0.2)
Renal impairment	1 (0.2)	1 (0.2)
Proteinuria	2 (0.4)	0
Oliguria	1 (0.2)	0

SMQ = Standardized MedDRA Query

Changes in Blood Urea Nitrogen and Serum Creatinine





*P<0.05 between groups (t-test for left panel, Chi-square for right panel)

Overview of Presentation

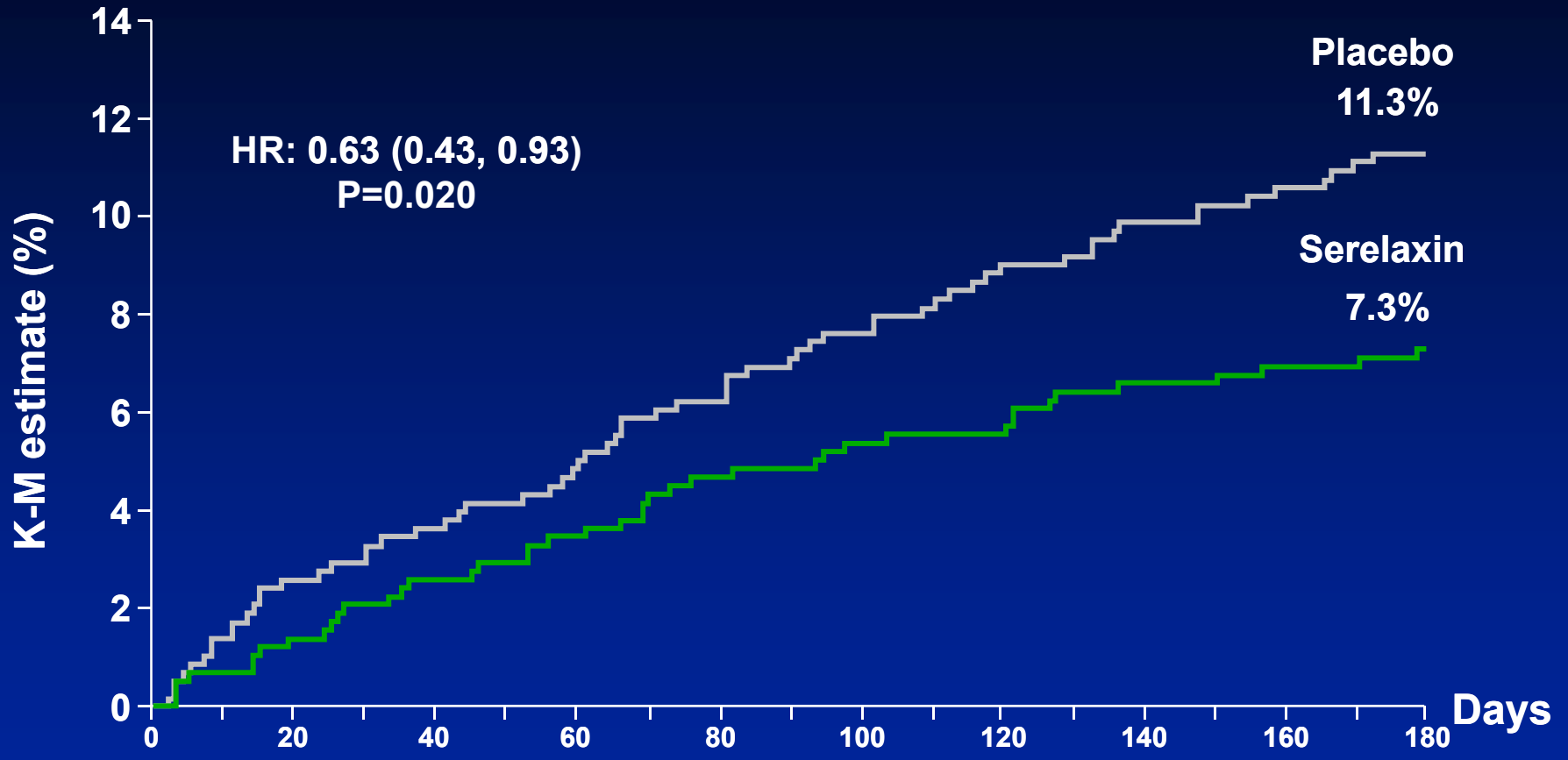
- RELAX-AHF Trial
  - Secondary endpoints
  - Other efficacy endpoints
  - Evaluation of safety
  - Cardiovascular and all-cause mortality
- Pre-RELAX-AHF Trial
- Benefit-to-Risk

Cardiovascular Mortality Through Day 180

Serelaxin	581	563	555	546	542	536	463
Placebo	580	559	547	535	523	514	444

The hazard ratio and CI based on a Cox regression model with treatment as a factor
P value by log rank test

All-Cause Mortality Through Day 180

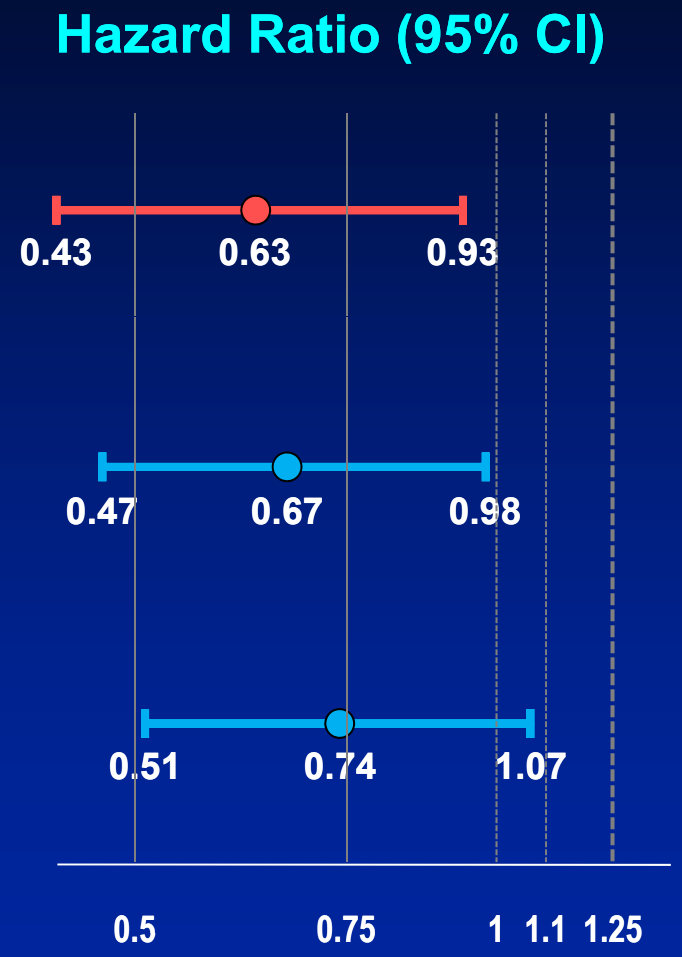


Serelaxin	581	563	555	546	542	536	463
Placebo	580	559	547	535	523	514	444

The hazard ratio and CI based on a Cox regression model with treatment as a factor
P value by log rank test

No Harm on 180-Day All-Cause Mortality Regardless of Handling of Non-Completers

	Deaths	
	Placebo	Serelaxin
Pre-specified analysis (non-completers censored)	65	42
All non-completers dead	72	49
Non-completers dead in serelaxin group and alive in placebo group	65	49



The vital status at 180 days could not be ascertained in 14 patients (12 patients withdrew from follow-up and 2 were lost to follow-up) with equal distribution between serelaxin (n=7) and placebo (n=7) groups

RELAX-AHF: Consistent Pattern of Benefit Across Multiple Clinical Endpoints

- Improved in-hospital clinical course through a reduction in the risk of worsening heart failure
  - Improved scores on Visual Analog Scale
  - Better response for signs and symptoms
- Less use and more rapid taper of IV diuretics
- Shorter index hospital stay
- Favorable effect on cardiac and renal biomarkers reflecting injury or dysfunction
- Fewer adverse events related to heart failure or renal impairment
- Lower risk of cardiovascular and all-cause mortality at 180 days, indicative of no harm

Overview of Presentation

- RELAX-AHF Trial
  - Secondary endpoints
  - Other efficacy endpoints
  - Evaluation of safety
  - Cardiovascular and all-cause mortality
- Pre-RELAX-AHF Trial
- Benefit-to-Risk

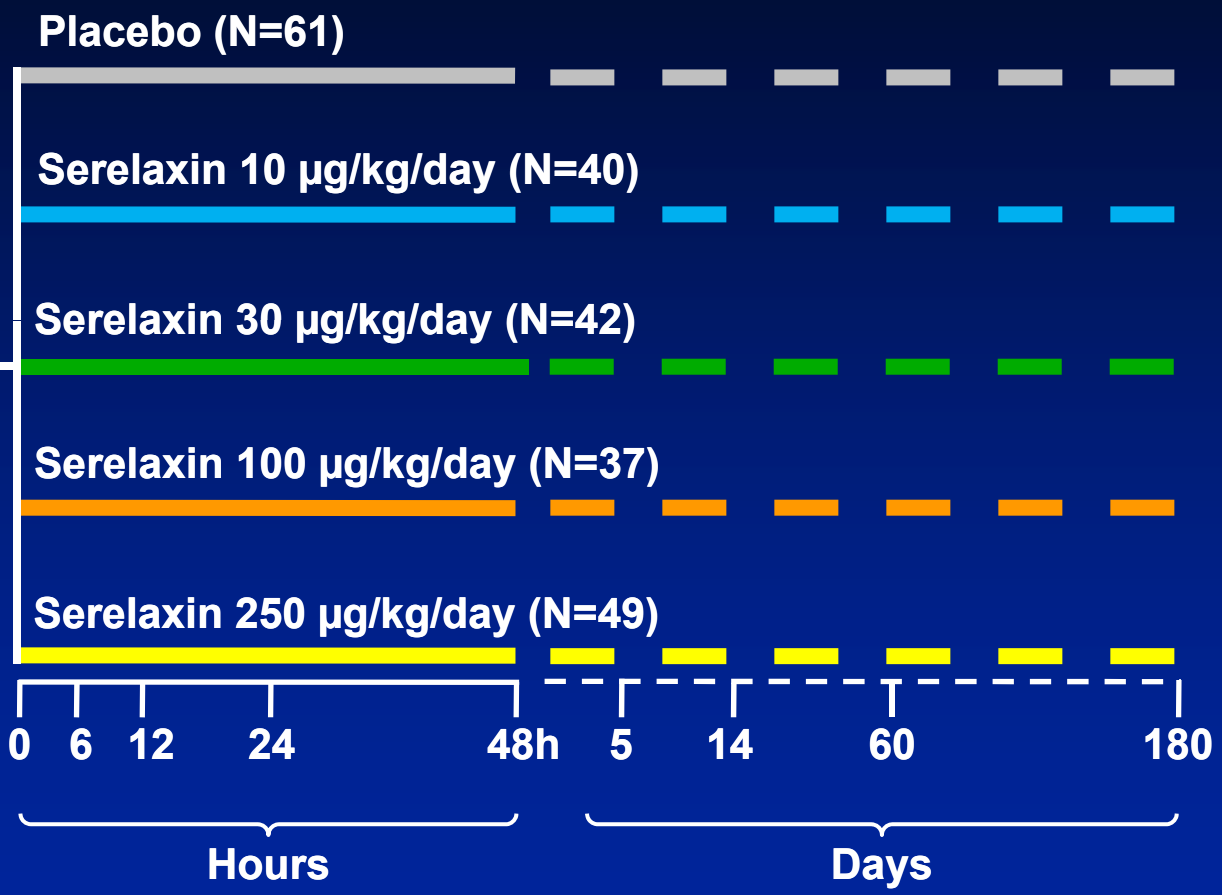
Pre-RELAX-AHF: Study Design

Acute heart failure (dyspnea, BNP, CXR)

Systolic BP >125 mmHg
CrCl 30-75 mL/min

After ≥40 mg IV furosemide

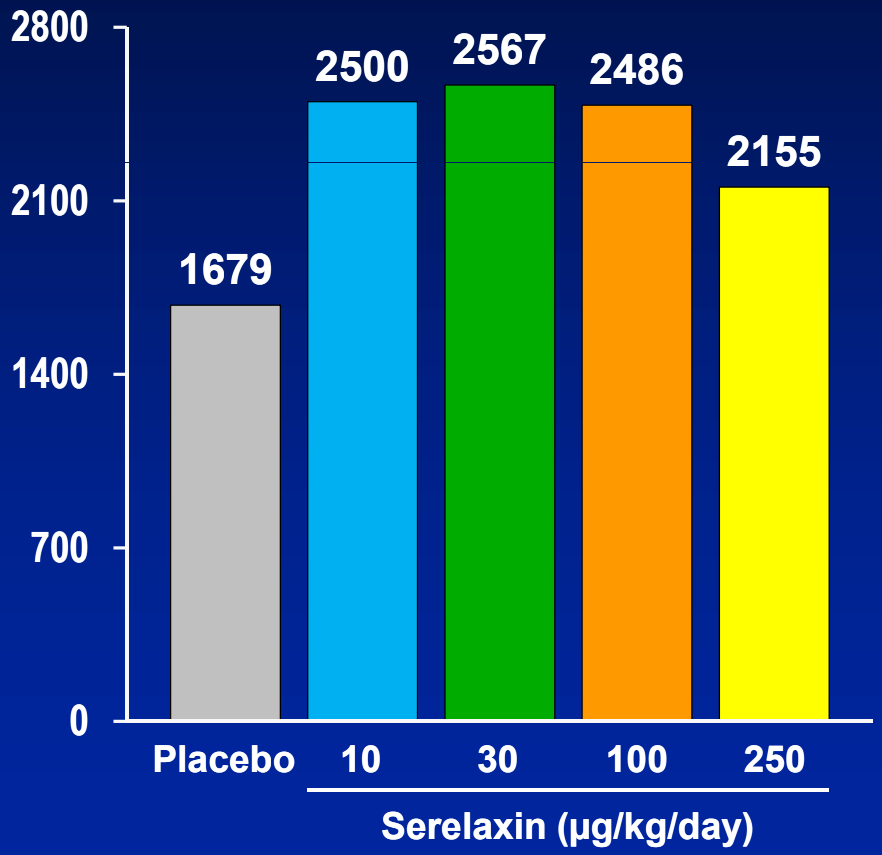
Within 16 hours of presentation



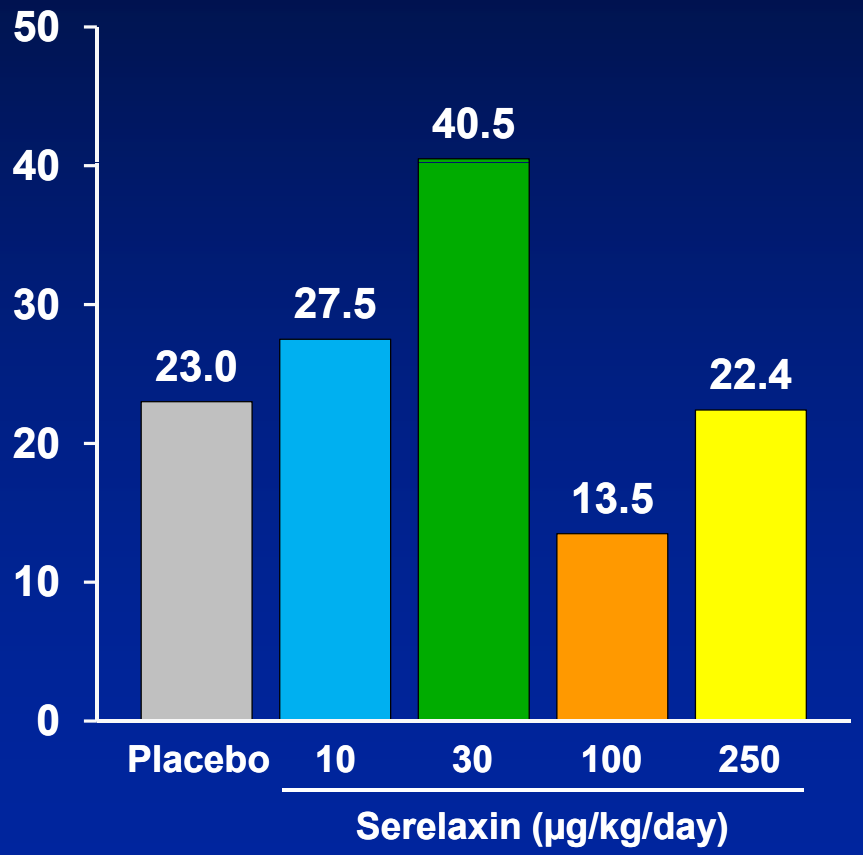
Randomization 3:2:2:2:2
48 h study drug infusion

Pre-RELAX-AHF: VAS AUC and Likert Responders

Visual Analog Scale AUC Through Day 5 (mm-hr)

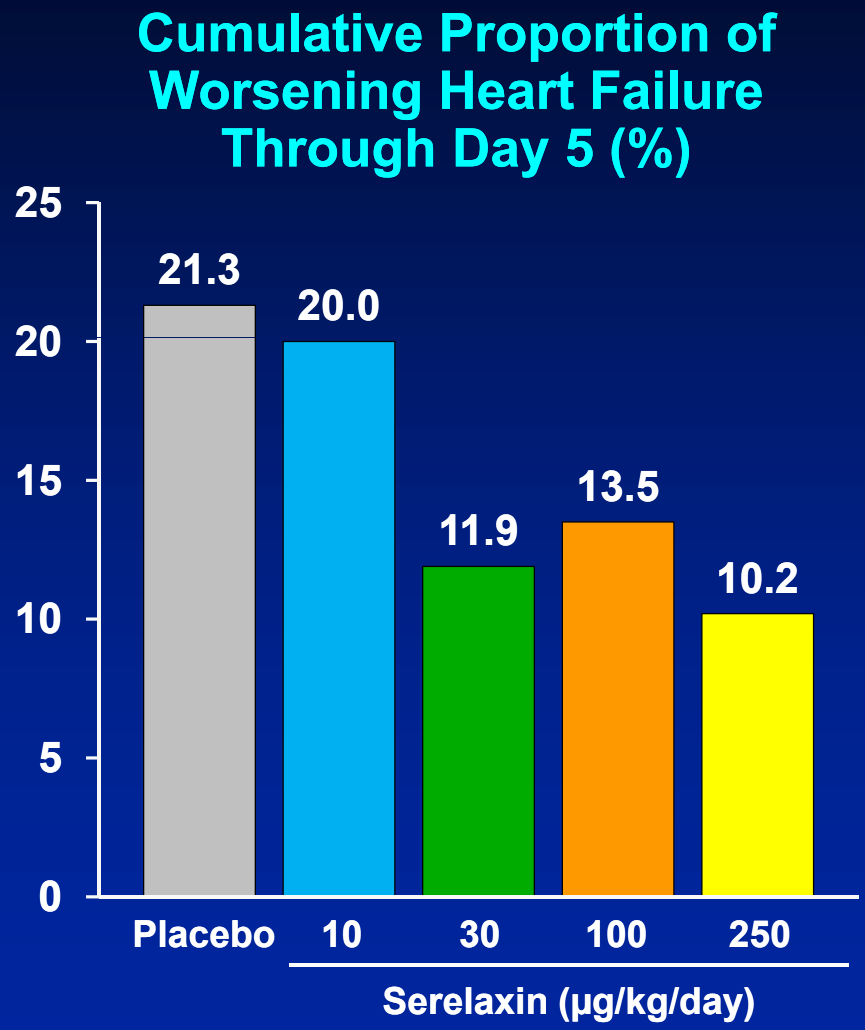


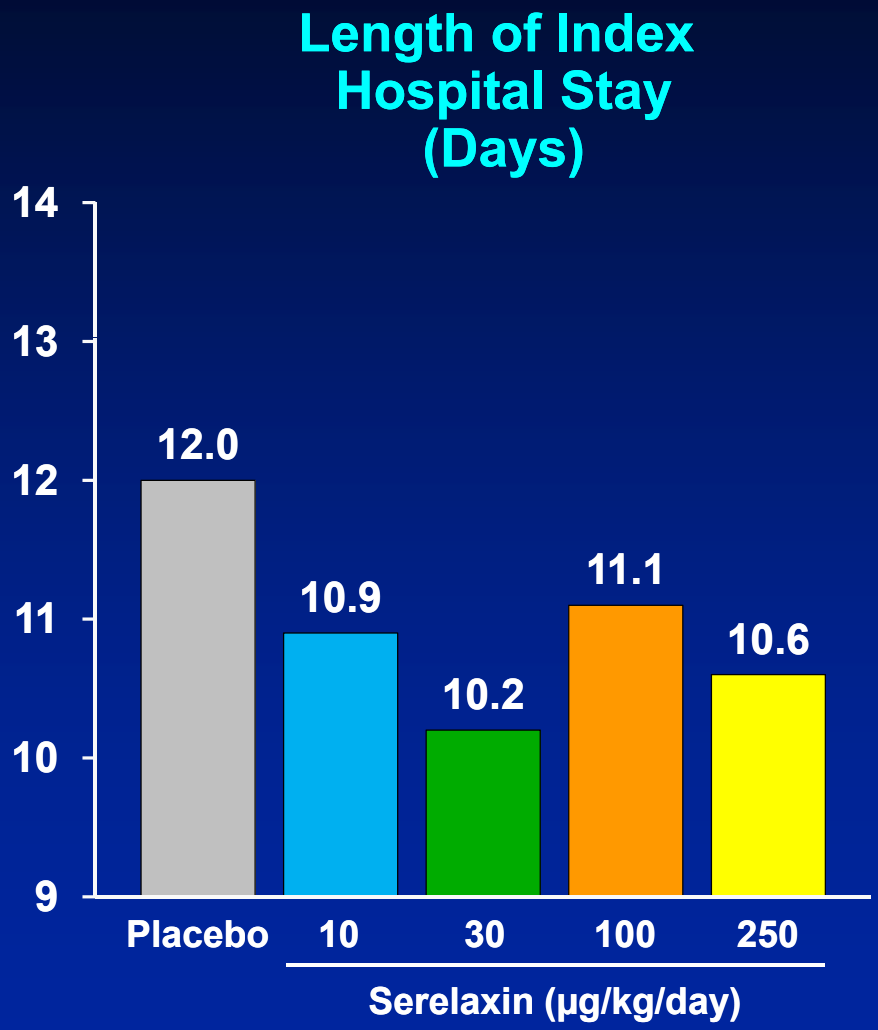
Proportion With Moderate/Marked Improvement on Likert Scale at 6h, 12h and 24h



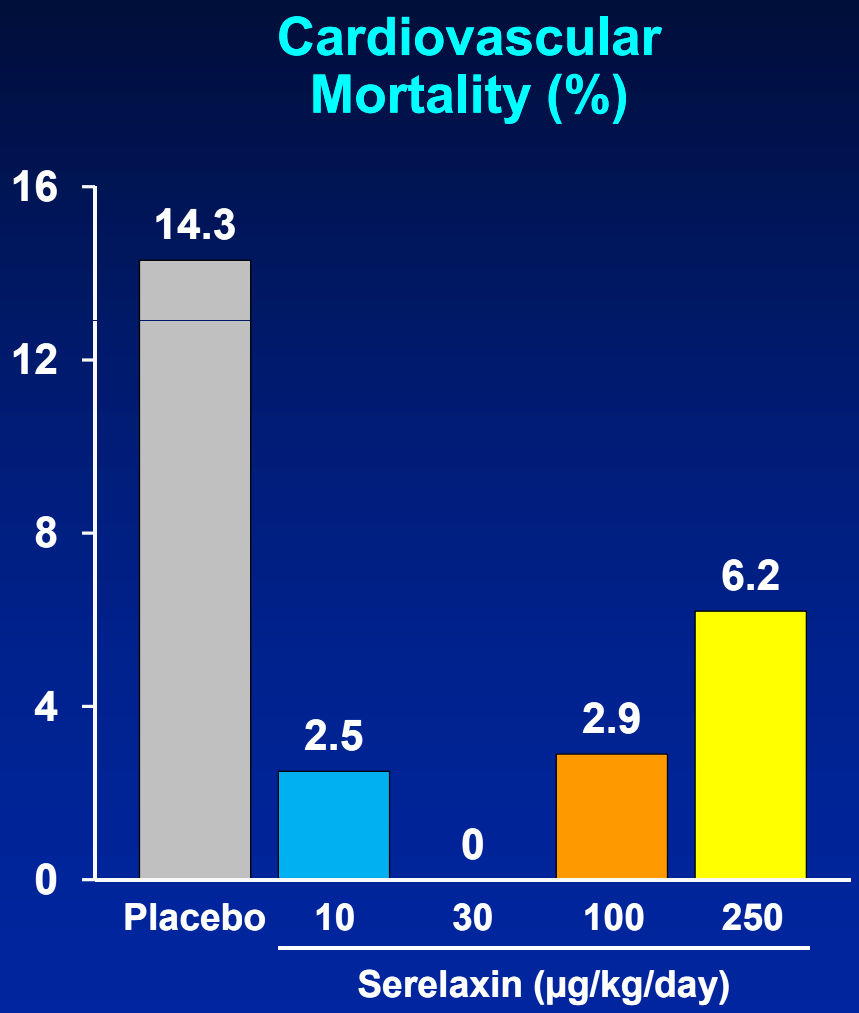
Teerlink et al., Lancet 2009; 373: 1429-39

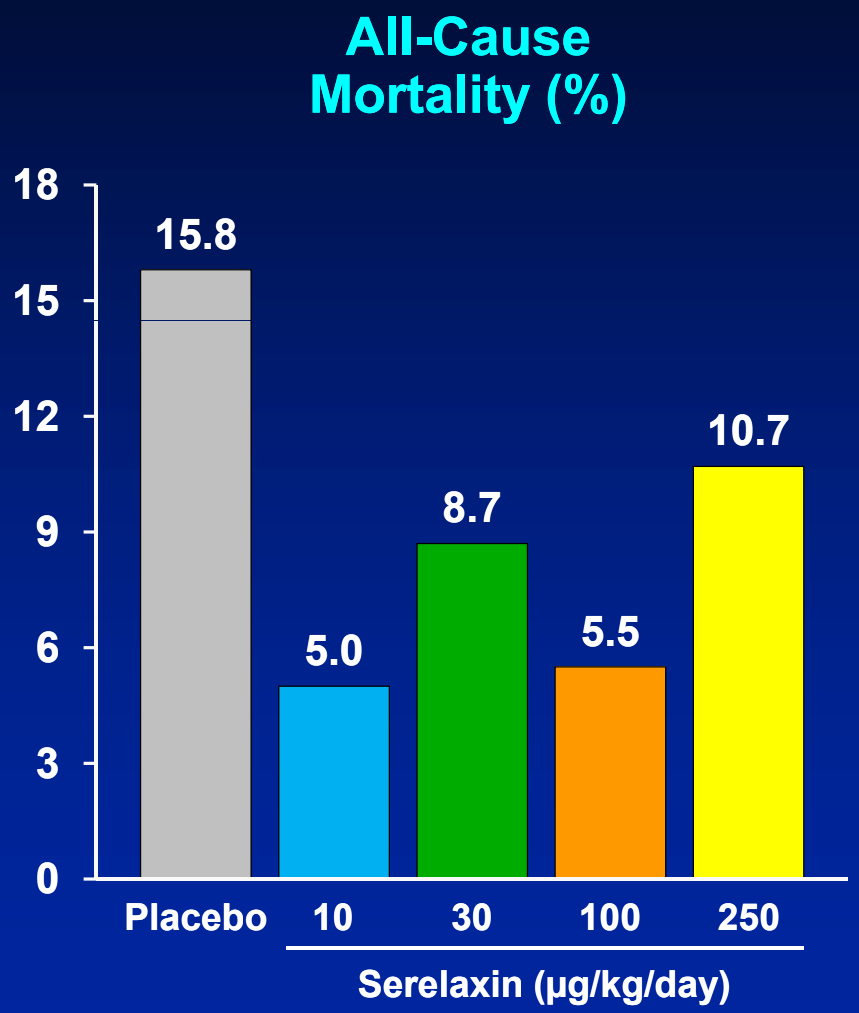
Pre-RELAX-AHF: Risk of Worsening Heart Failure and Length of Index Hospital Stay



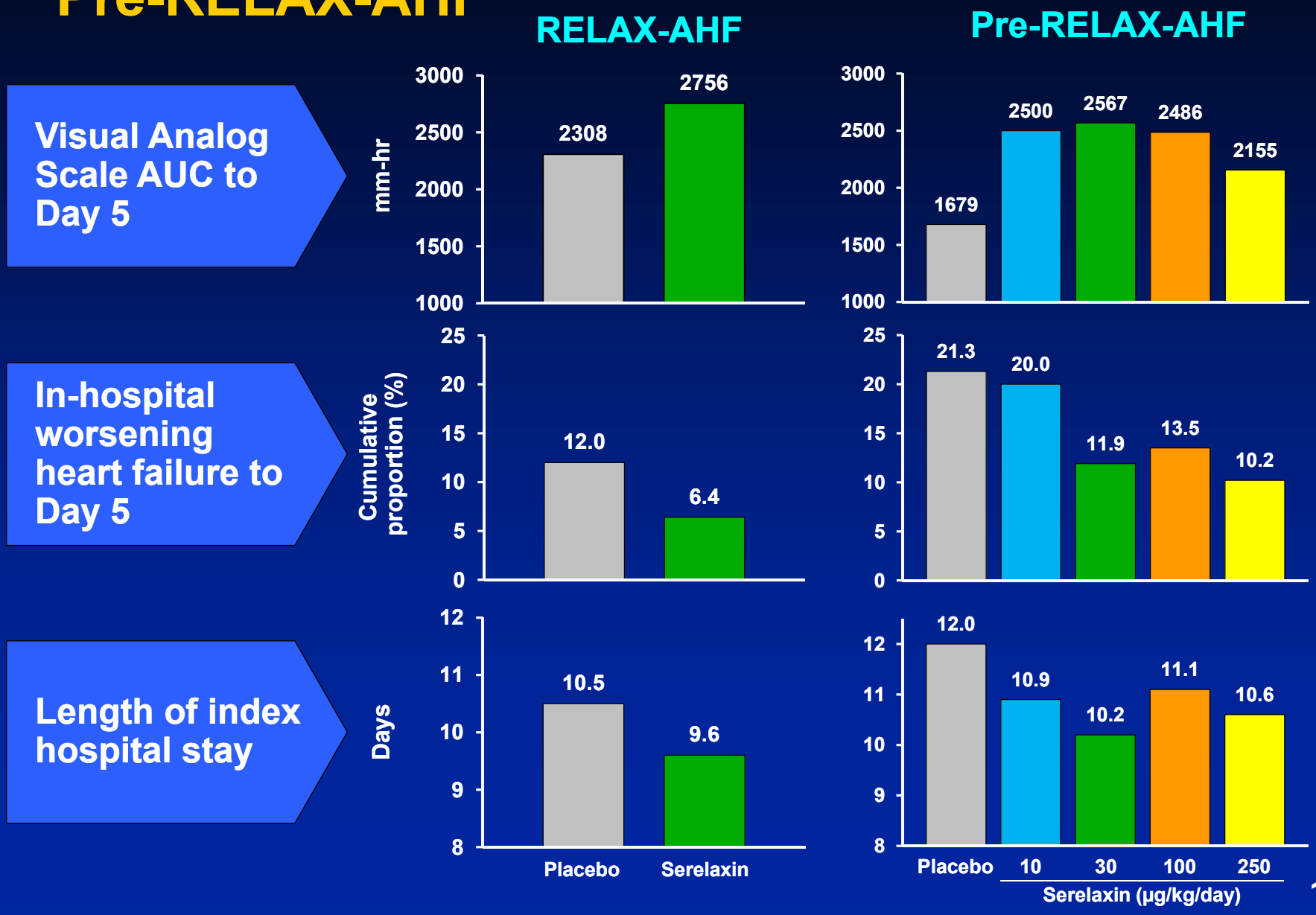


Pre-RELAX-AHF: Cardiovascular and All-Cause Mortality Through Day 180





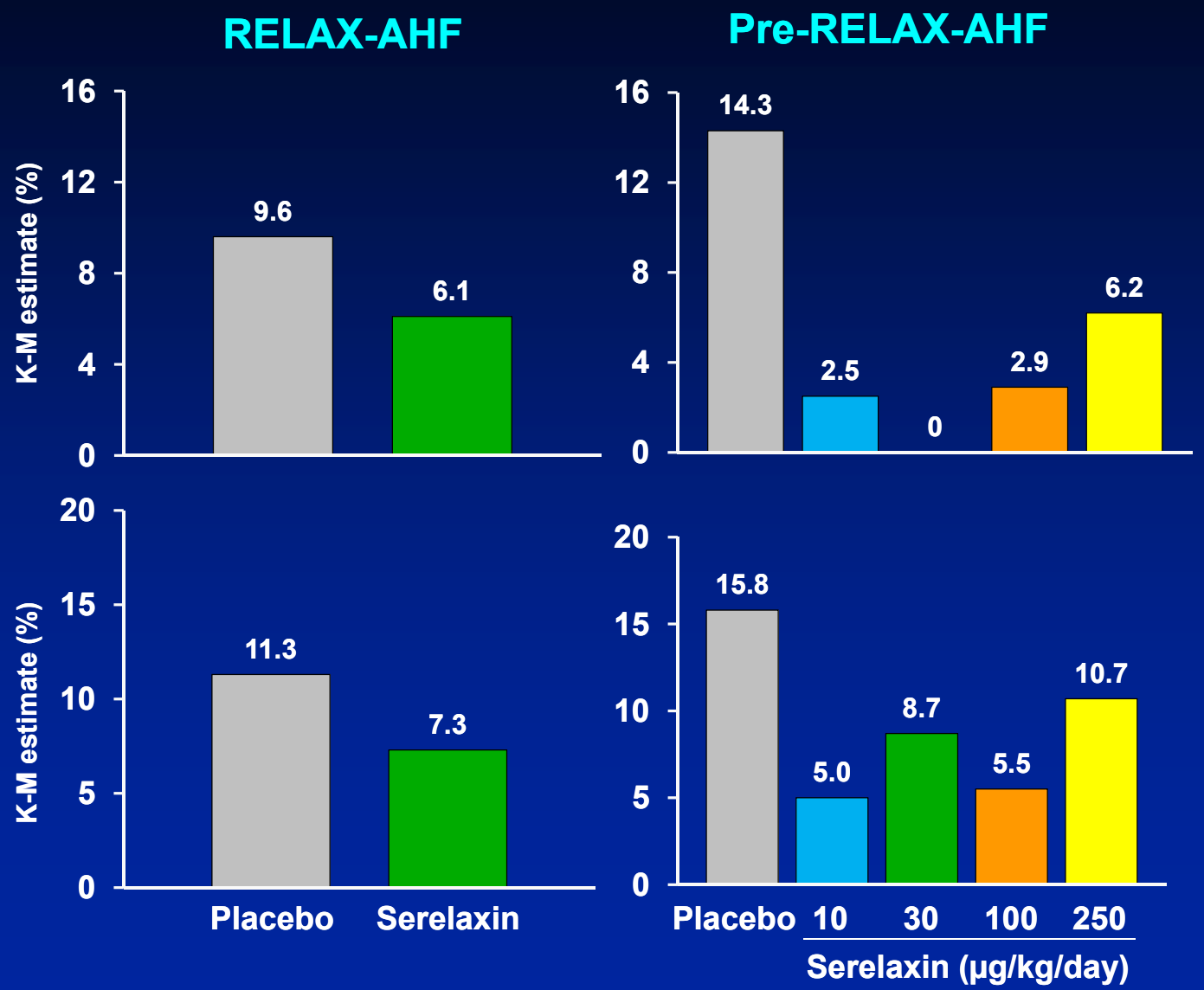
Consistency Across RELAX-AHF and Pre-RELAX-AHF



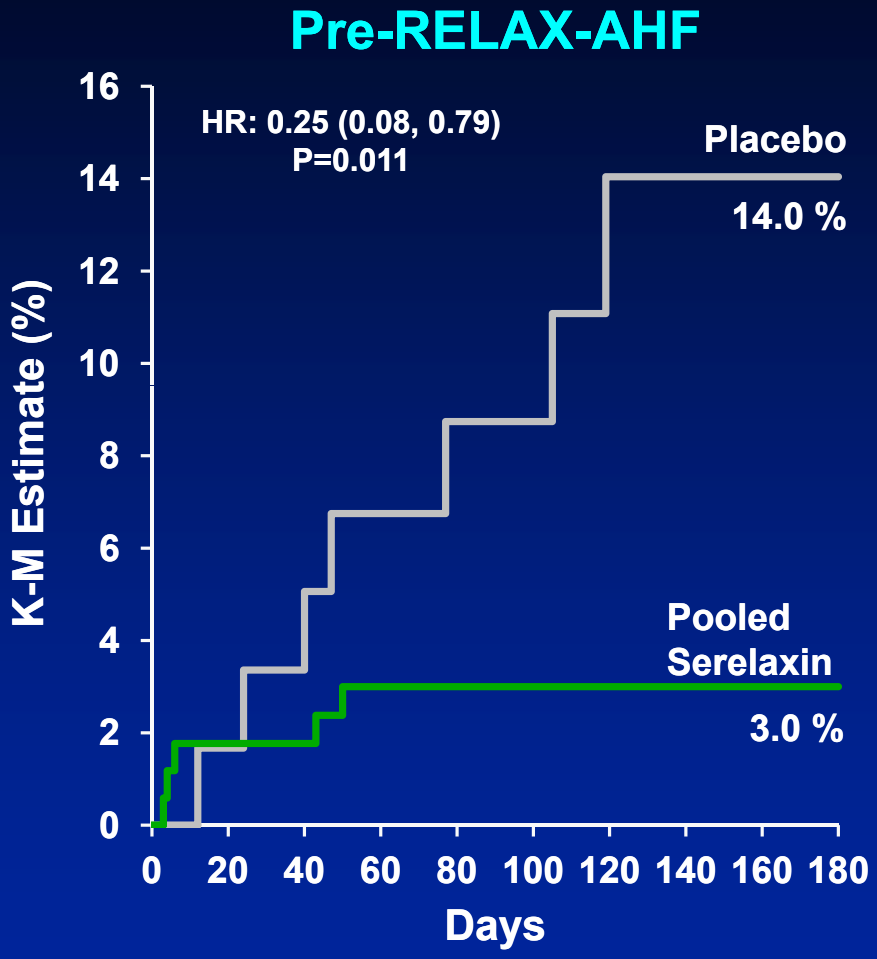
Consistency Across RELAX-AHF and Pre-RELAX-AHF

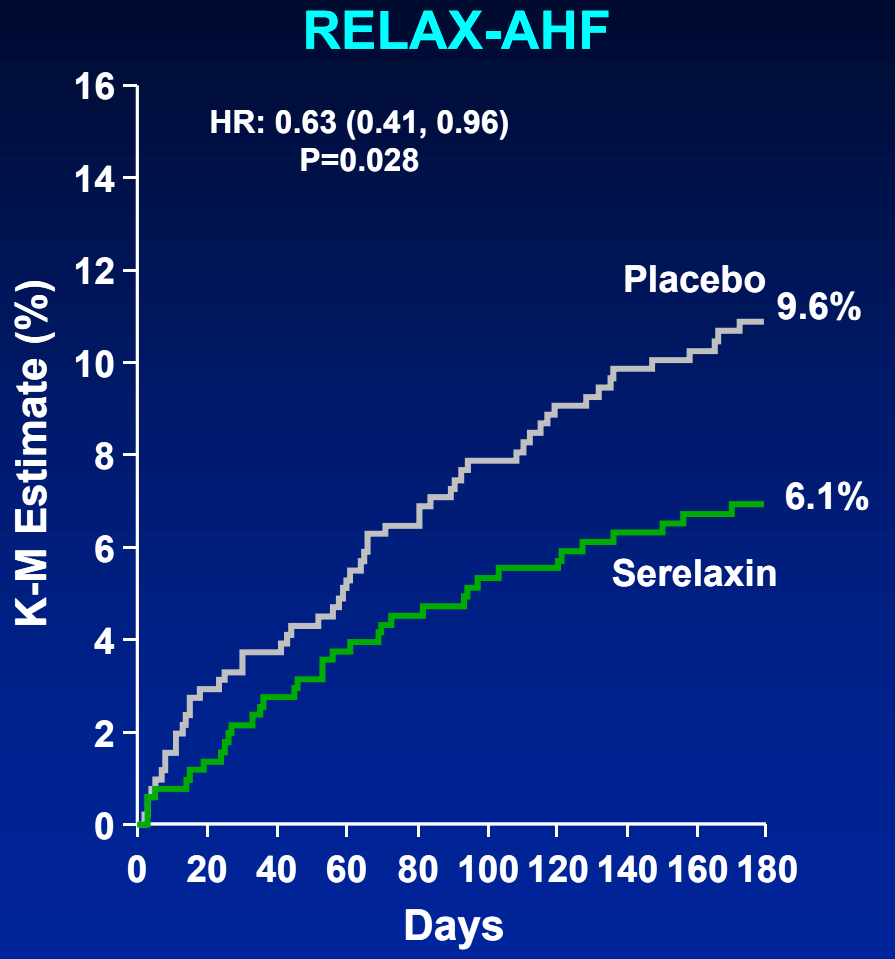
Cardiovascular mortality to Day 180

All-cause mortality to Day 180



Consistent Effect on 180-Day Cardiovascular Mortality





Pooled analysis Pre-RELAX-AHF (all doses) and RELAX-AHF

- **Cardiovascular mortality HR: 0.55, P=0.0044**
- **All-cause mortality HR: 0.62, P=0.0081**

High Degree of Consistency Between Pre-RELAX-AHF and RELAX-AHF

- Near identical design
  - Both trials had similar populations, durations of treatment and follow-up, and efficacy endpoints
- Pre-RELAX-AHF
  - Concordant treatment effect across multiple endpoints
  - Consistent treatment effect across multiple doses
- RELAX-AHF confirms Pre-RELAX-AHF
  - Concordant treatment effect across multiple endpoints
  - Concordant with treatment effects in Pre-RELAX-AHF

Overview of Presentation

- RELAX-AHF Trial
  - Secondary endpoints
  - Other efficacy endpoints
  - Evaluation of safety
  - Cardiovascular and all-cause mortality
- Pre-RELAX-AHF Trial
- Benefit-to-Risk

Favorable Benefit-to-Risk for Serelaxin in Patients With Acute Heart Failure

Benefits

- Improved clinical course through a reduction of in-hospital worsening heart failure
- Less use of IV diuretics and rescue therapy
- Shorter length of index hospital stay

Risks

- Manageable decreases in blood pressure
- No adverse long-term effects

Conclusion

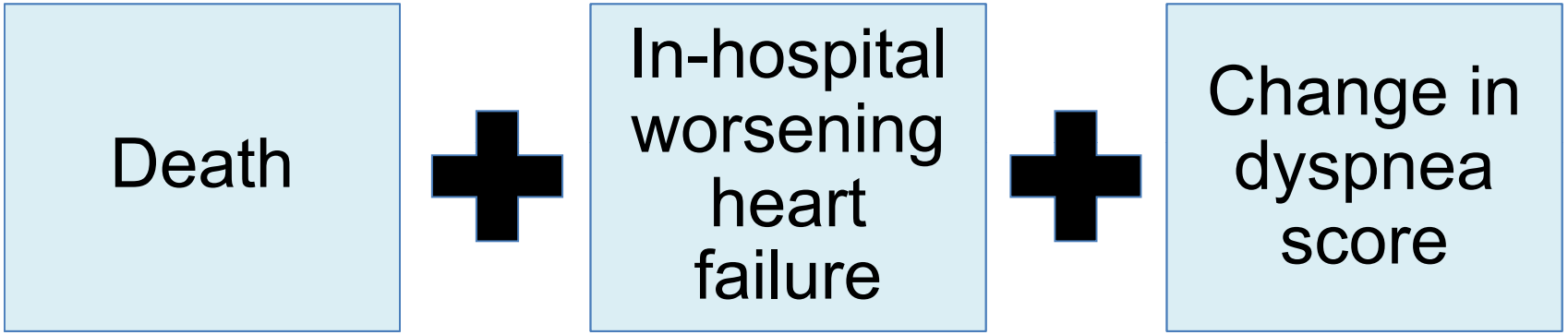
In light of the ***consistent and robust*** demonstration of clinically relevant benefits ***within*** and ***across*** trials, with minimal risks, the totality of evidence supports the proposed indication for use:

Serelaxin is indicated to improve the symptoms of acute heart failure through reduction of the rate of worsening heart failure

A Clinical and Regulatory Perspective

Milton Packer, M.D.
University of Texas Southwestern Medical Center
Dallas, Texas

Visual Analog Scale Area Under the Curve Is a Composite Endpoint



If a trial demonstrates an effect on a composite endpoint, it is important (1) to ensure that the effects on each component are directionally concordant and (2) to identify which component(s) drive the effect.

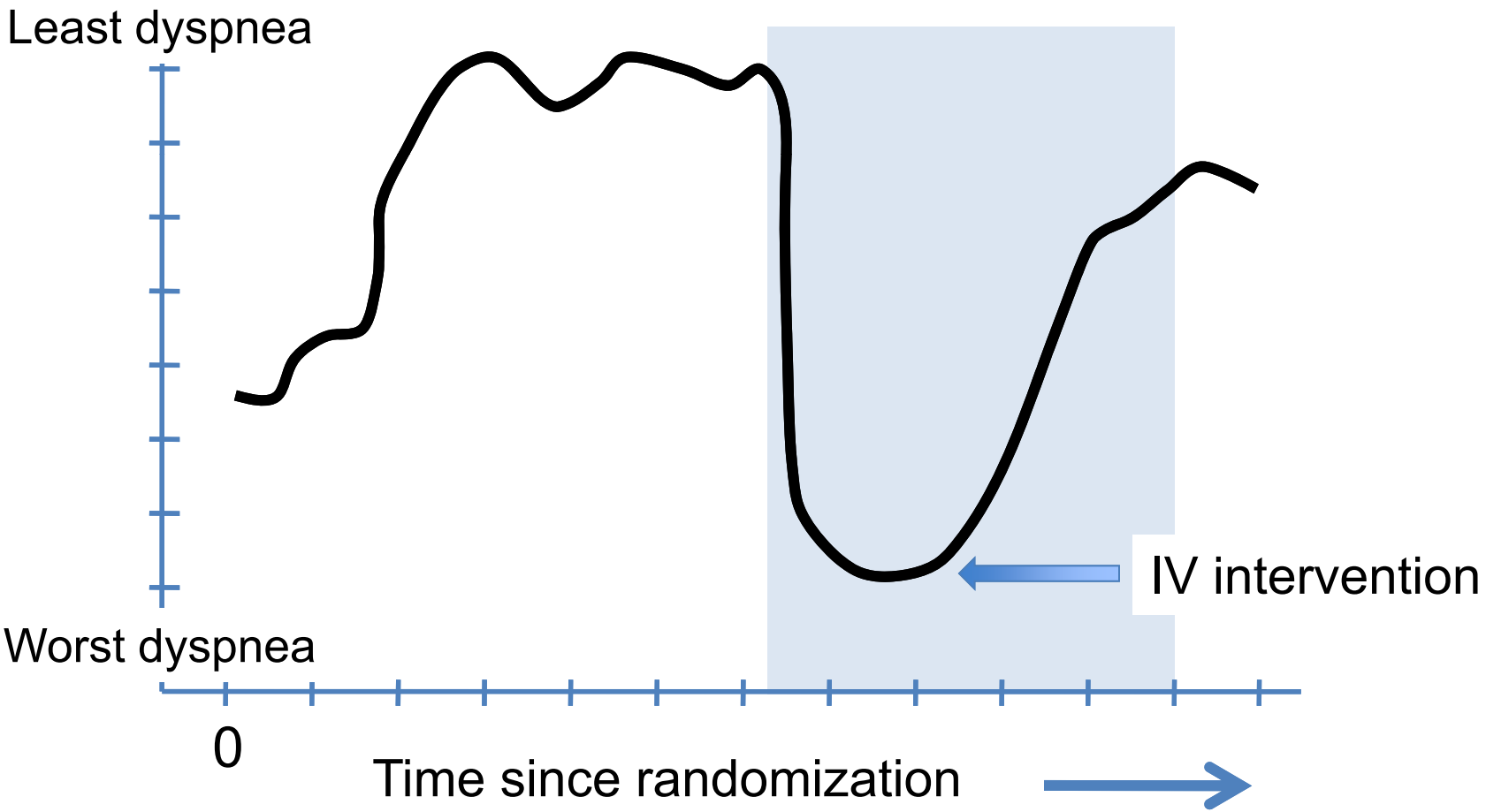
Visual Analog Scale Area Under the Curve Is a Composite Endpoint

If a trial demonstrates an effect on a composite endpoint, it is important (1) to ensure that the effects on each component are directionally concordant and (2) to identify which component(s) drive the effect.

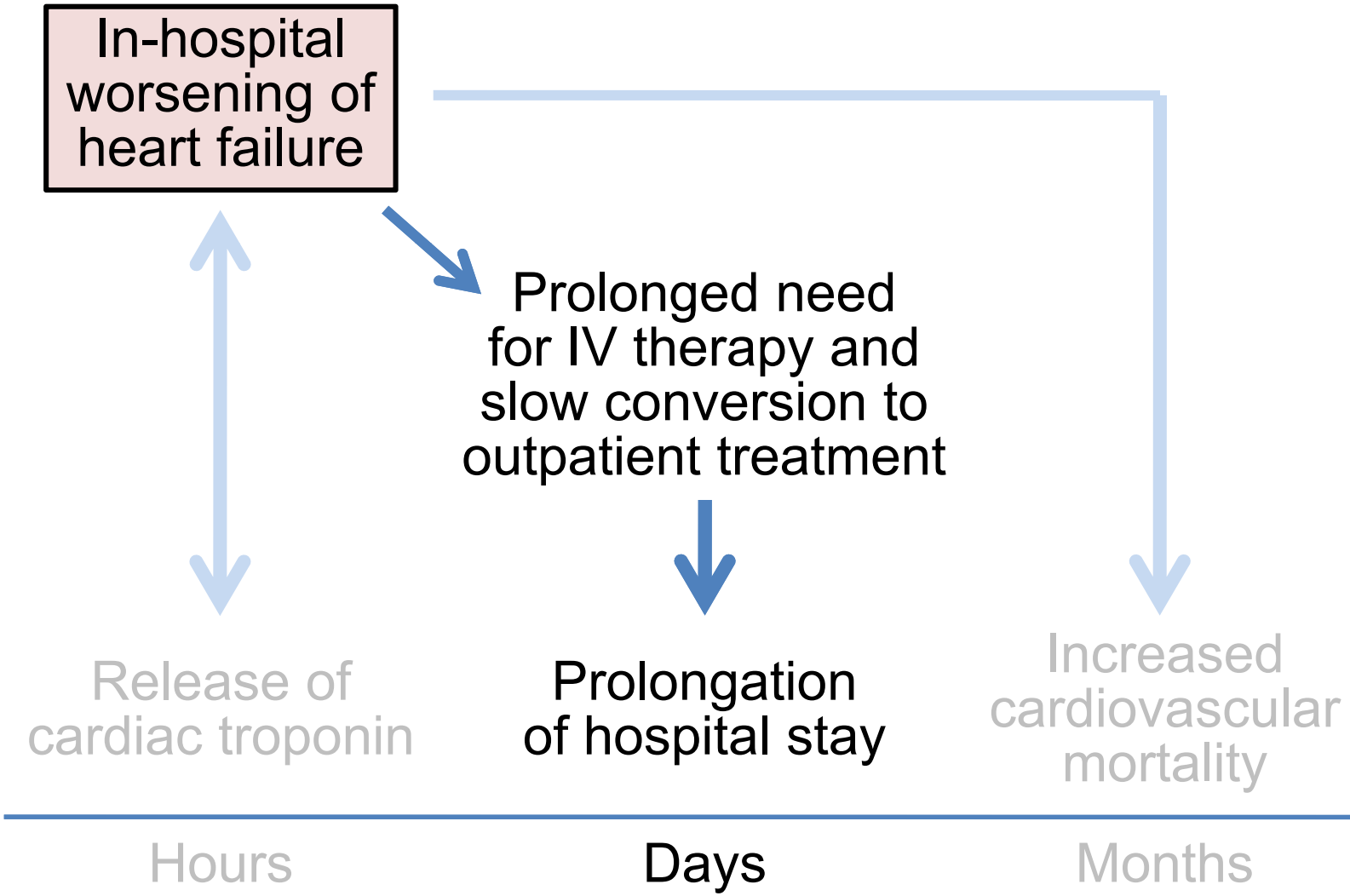
Effect of Serelaxin on the Risk of In-Hospital Worsening Heart Failure

- Is the effect of serelaxin on in-hospital worsening heart failure ***meaningful***?

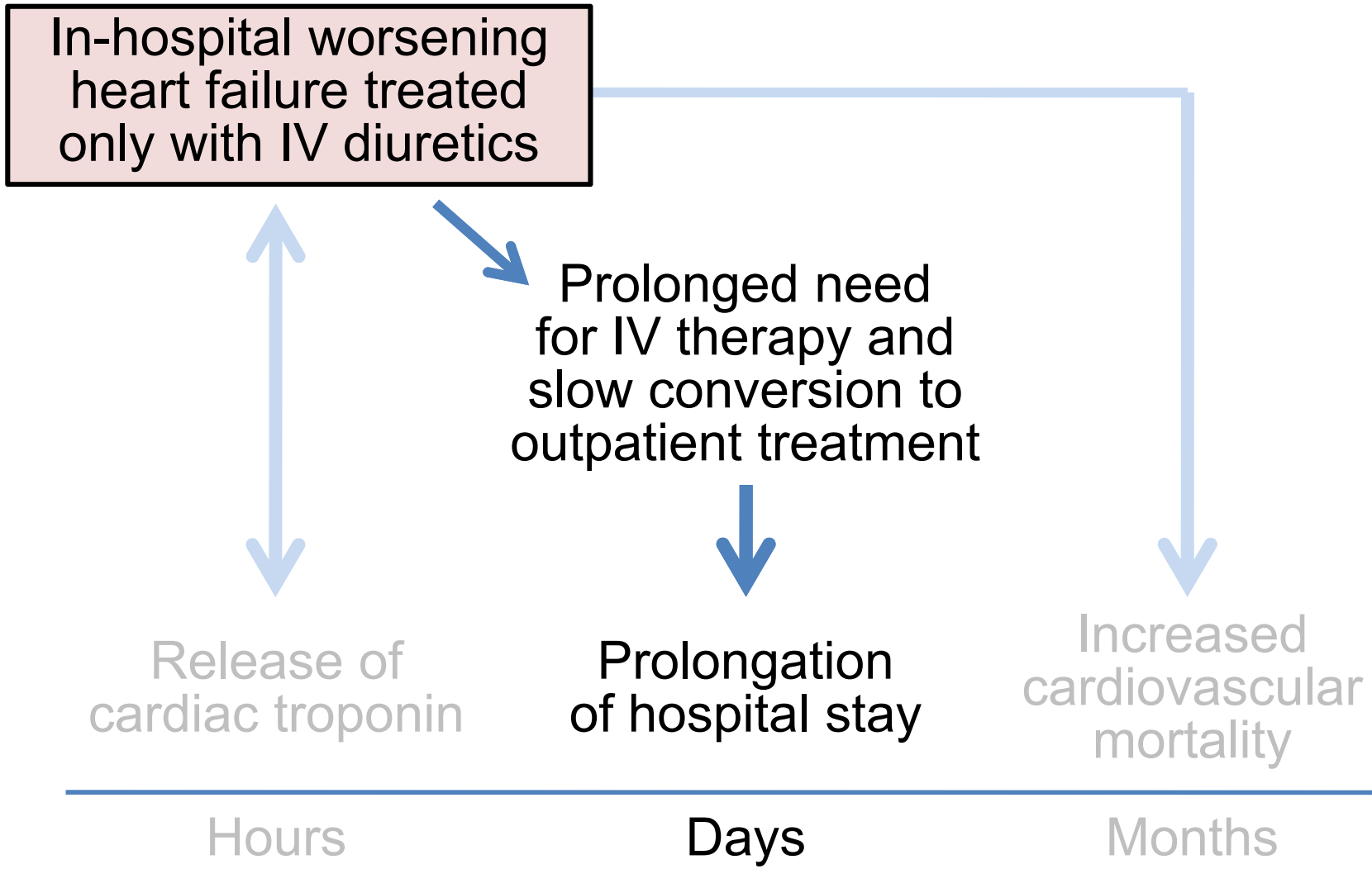
In-Hospital Worsening Heart Failure Represents Failure of Prescribed Therapy to Maintain Clinical Stability



Worsening Heart Failure Reflects ***Treatment Failure*** on Conventional Therapy



Worsening Heart Failure Treated Only With IV Diuretics Reflects ***Treatment Failure***



In-Hospital Worsening Heart Failure Has Been Analyzed as a Treatment Failure

	Drug	In-hospital worsening heart failure incorporated into symptom endpoint
EVEREST	Tolvaptan	No
ASCEND	Nesiritide	No
VERITAS	Tezosentan	Worst rank or score
PROTECT	Rolofylline	Worst rank or score
REVIVE	Levosimendan	Worst rank or score
RELAX-AHF	Serelaxin	Worst rank or score
TRUE-AHF	Ularitide	Worst rank or score

Composite Endpoints in Acute Heart Failure

Visual Analog Scale With Worst Score Assignment	Clinical Composite (Acute Heart Failure)
No dyspnea ↑ Visual Analog Scale Area Under Curve ↓ Severe dyspnea	Moderate or marked improvement in symptoms at all planned assessments without in-hospital worsening heart failure or death
	Modest improvement or worsening of symptoms
	Moderate or marked worsening of symptoms at any planned assessment
Worsening heart failure requiring IV or mechanical interventions	Unresponsive or worsening heart failure requiring IV or mechanical interventions
Death	Death

Effect of Serelaxin on the Risk of In-Hospital Worsening Heart Failure

- Is the effect of serelaxin on in-hospital worsening heart failure ***meaningful***?
- Is the effect of serelaxin on in-hospital worsening heart failure ***robust***?

Effect of Serelaxin on First and Recurrent In-Hospital Worsening Heart Failure and Death

	Placebo (n=570)	**Serelaxin** (n=568)
Number of patients with at least one episode of in-hospital worsening heart failure or death	**69**	**37**
Number of patients with recurrent episodes of in-hospital worsening heart failure or death	**15**	**4**
Number of deaths and episodes of in-hospital worsening heart failure	**84**	**41**

All analyzed were performed for the first 5 days following randomization

Interventions for Worsening Events That Were Meaningful Departure From Ongoing Therapy

	Placebo (n=580)	Serelaxin (n=581)
Patients with WHF event in analysis of 5-day primary endpoint	**69**	**37**
Patients who died or who experienced WHF leading to rehospitalization	**5**	**4**
Patients with WHF event treated with IV positive inotropic drug or mechanical intervention	**17**	**6**
Patients with WHF event who received new treatment with IV nitrates or IV nitroprusside	**13**	**7**
Patients with WHF event treated with reinitiation or doubling of daily dose of IV diuretic	**14**	**7**
Total	**49**	**24**

P=0.003

All events occurred within 5-day primary endpoint period

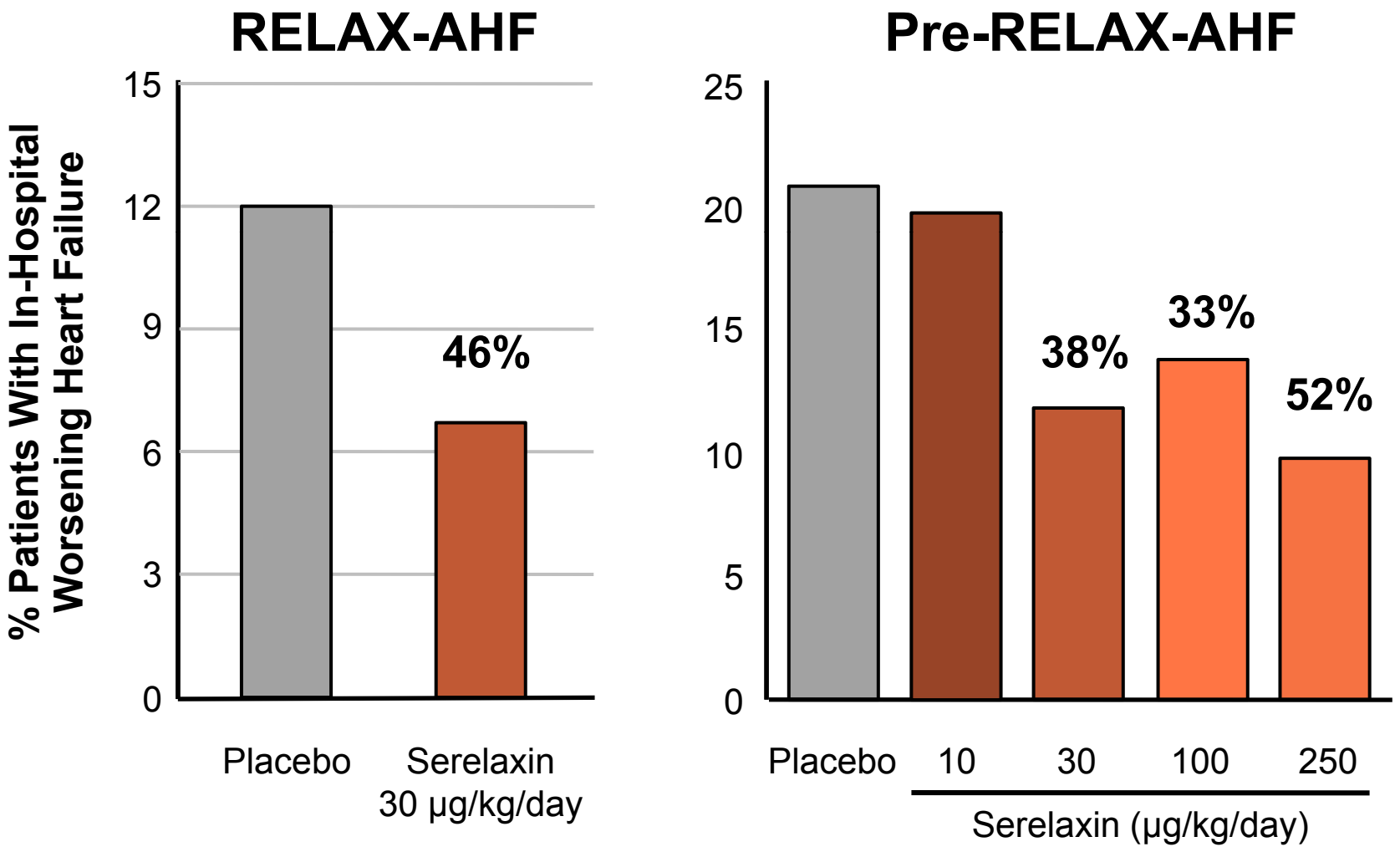
Did Serelaxin Prevent Only Mild Worsening Events Treated With IV Diuretics?

All Worsening Events Through Day 5

	Severity	Placebo	Serelaxin
IV inotropes or mechanical support	**Mild**	**1**	**0**
	Moderate	**10**	**1**
	Severe	**6**	**5**
IV nitrates with or without IV diuretics	**Mild**	**5**	**1**
	Moderate	**7**	**6**
	Severe	**5**	**2**
IV diuretics only	**Mild**	**13**	**6**
	Moderate	**25**	**15**
	Severe	**3**	**1**

Patients who died or rehospitalized without prior WHF events were excluded

Effect on In-Hospital Worsening Heart Failure in RELAX-AHF and Pre-RELAX-AHF Trials



Consistency of Effect of Serelaxin Across Endpoints, Trials and Doses

RELAX-AHF		Pre-RELAX-AHF			
30		10	30	100	250
↑	Visual Analog Scale AUC up to Day 5	↑	↑	↑	↑
↓	In-hospital worsening heart failure during first 5 days		↓	↓	↓
↓	Length of index hospital stay	↓	↓	↓	↓

Effect of Serelaxin on the Numerical Assessment of Clinical Course

Serelaxin favorably influenced the VAS AUC primary endpoint (P=0.0075).

This was achieved by assigning the same worst score (zero) to all patients with worsening heart failure regardless of the gravity of the event and the intensity and aggressiveness of treatment.

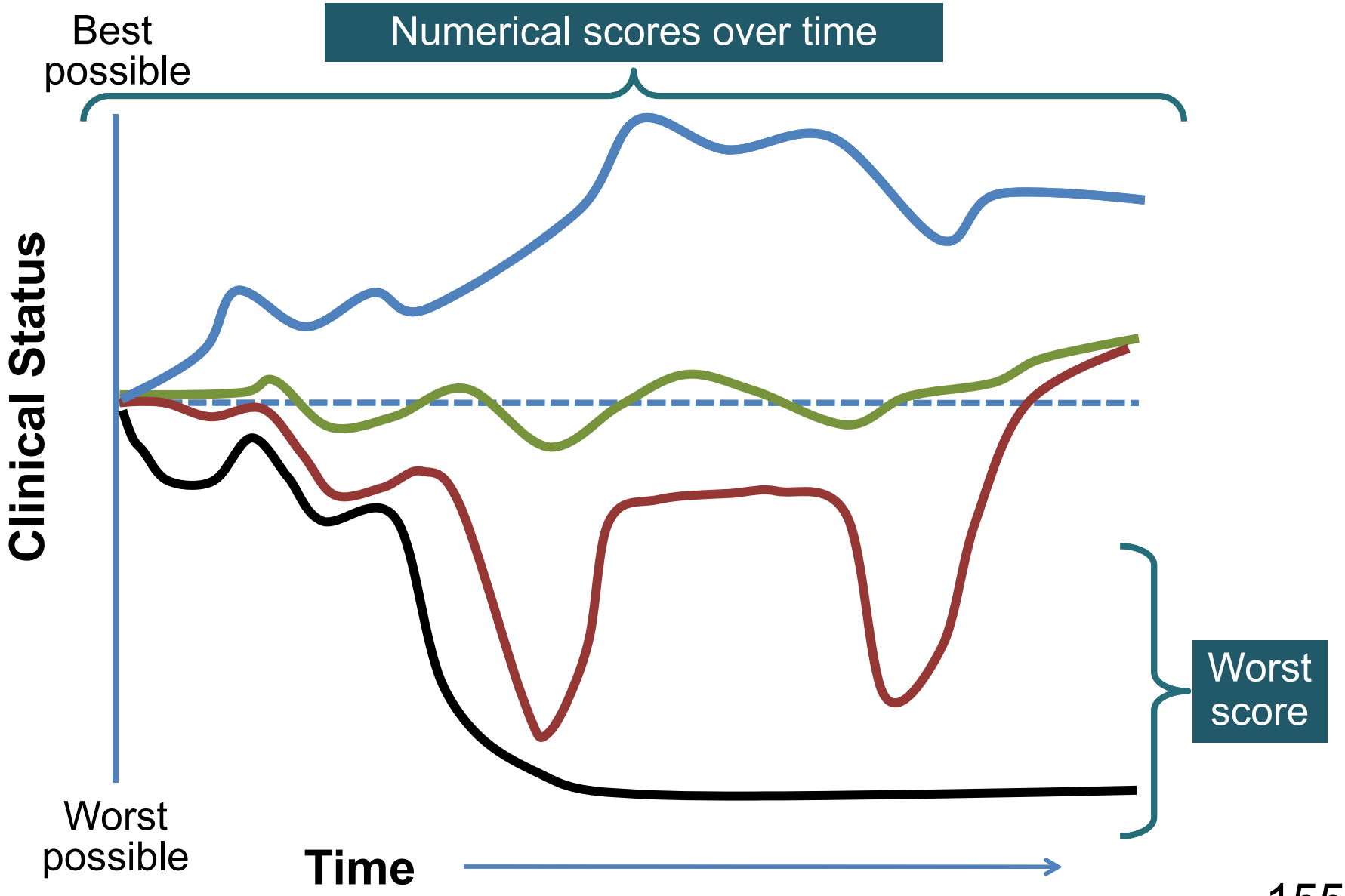
The FDA wonders: Was that a reasonable thing to do? Would the results differ if some other approach had been used?

FDA Review Document

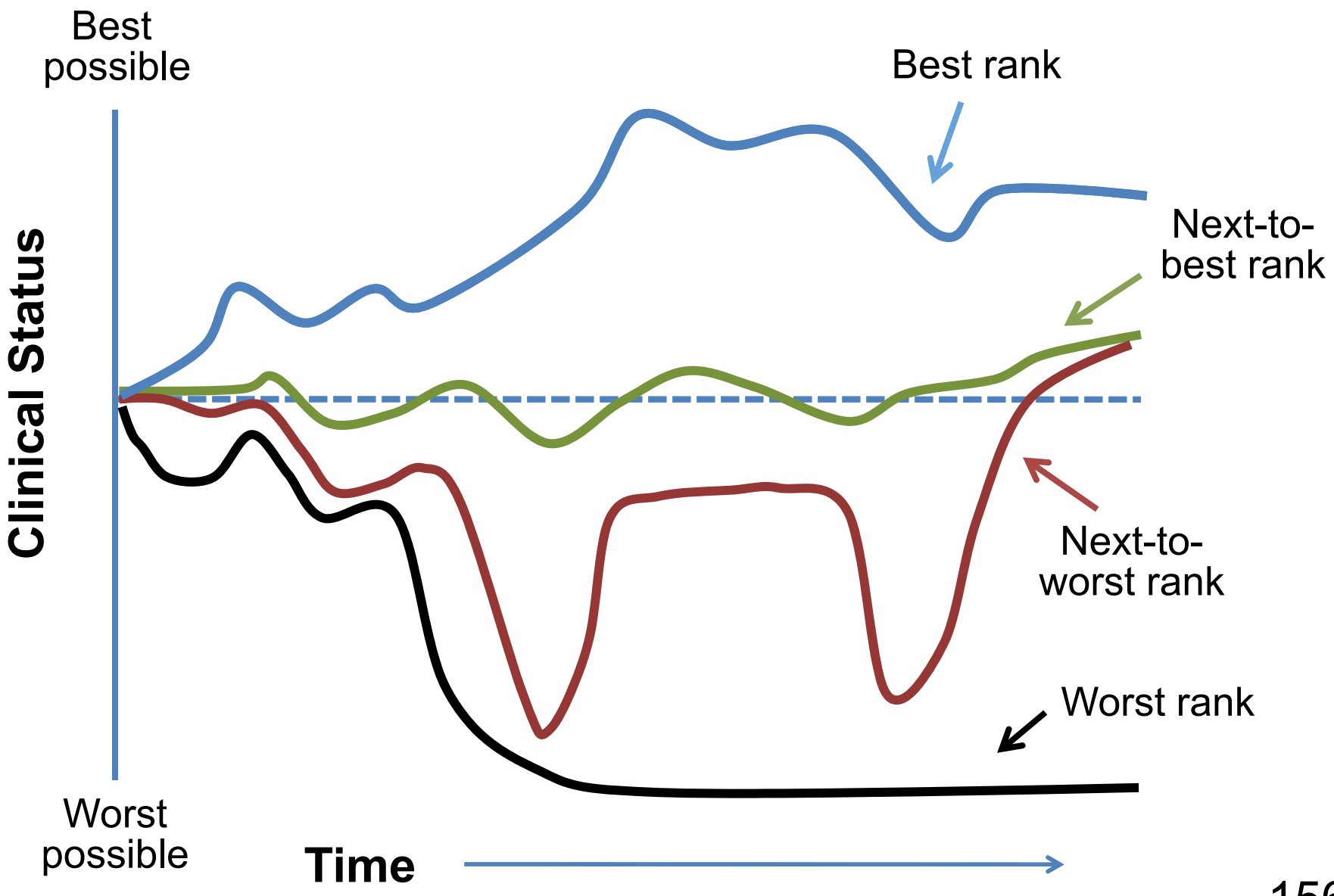
In its Review Document, the FDA asks . . .

- Should patients with a worsening event have been assigned a zero score?
- Should the zero score have superseded future clinical assessments?
- Should patients with all types of worsening event have received the same zero score?

Numerical Assessment of Clinical Course



Ranking the Clinical Course of Patients



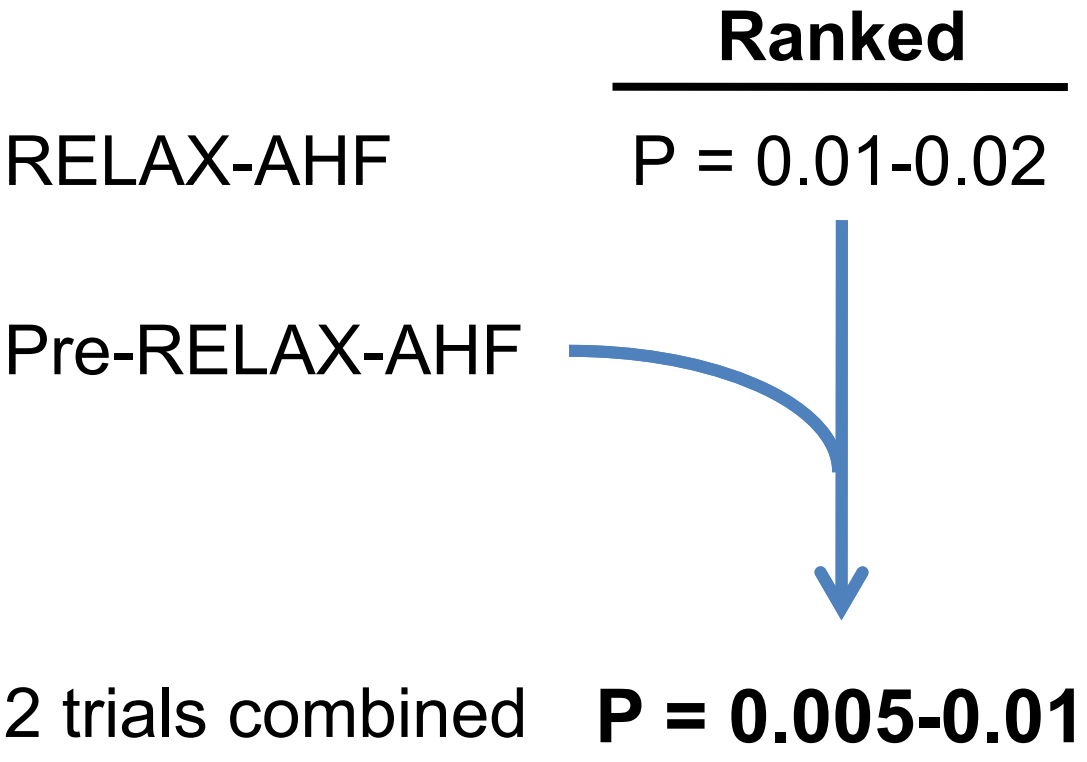
Primary Endpoint Analyses Based on Clinically Ranked Outcomes Without Use of Arbitrary Numerical Score Assignment

	P value
Log rank test of clinically ranked outcomes	
All worsening heart failure events assigned same rank	**0.0190**
Earlier worsening heart failure events assigned worse rank than later events	**0.0110***
Recurrent worsening events assigned worse rank than single events	**0.0150**
Aggressive interventions ranked worse than IV vasodilators, ranked worse than IV diuretics	**0.0183**
Prespecified t-test with zero score assignment	**0.0075**

*** In Novartis Briefing Book, other sensitivity analysis presented in addendum**

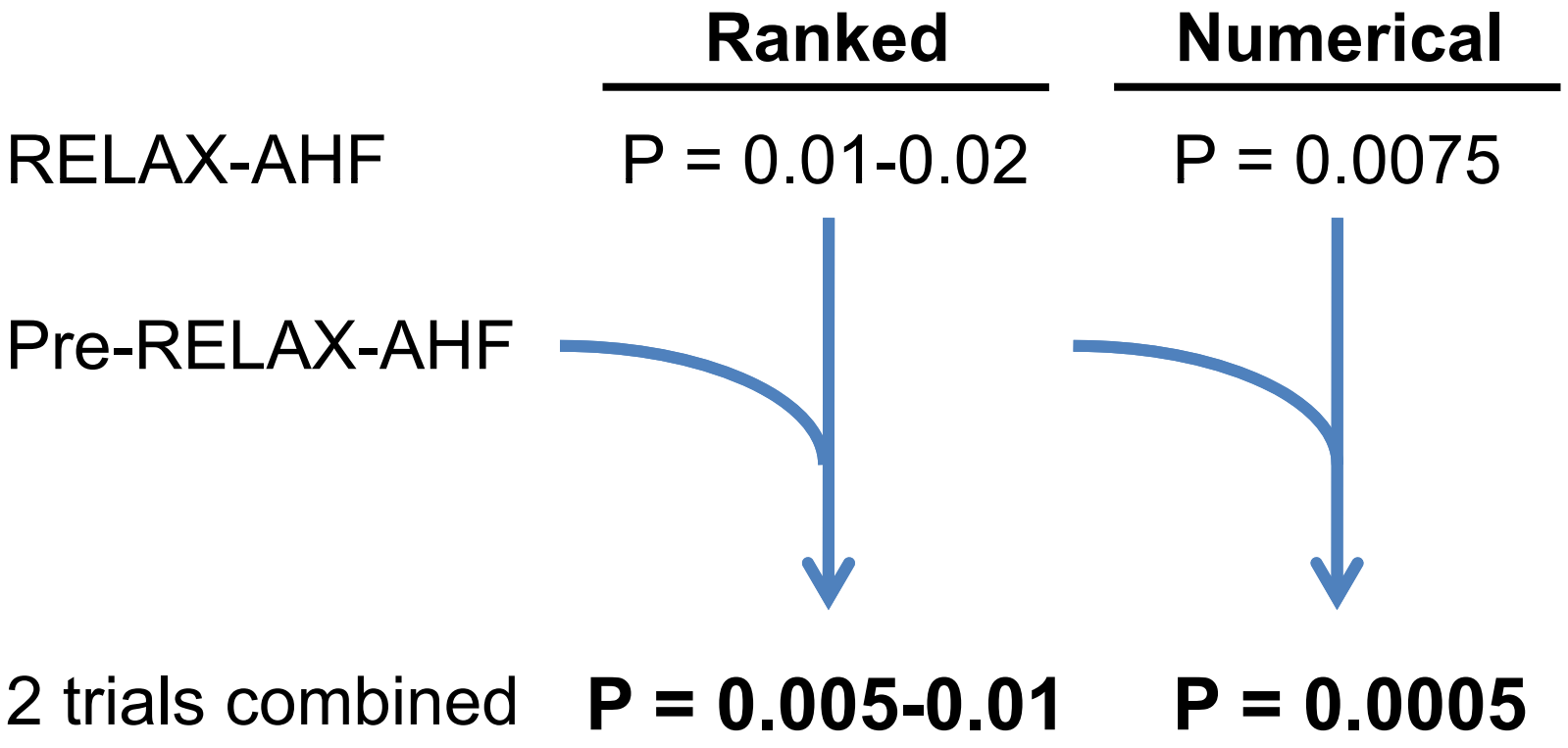
Worst rank is assigned to death (earlier worse than later) and best rank is assigned to patients without worsening event and is based on VAS AUC (better rank in patients with positive AUC than negative AUC)

Primary Endpoint Analyses Based on Ranked and Numerical Approach: Combined Analysis of Pre-RELAX-AHF and RELAX-AHF



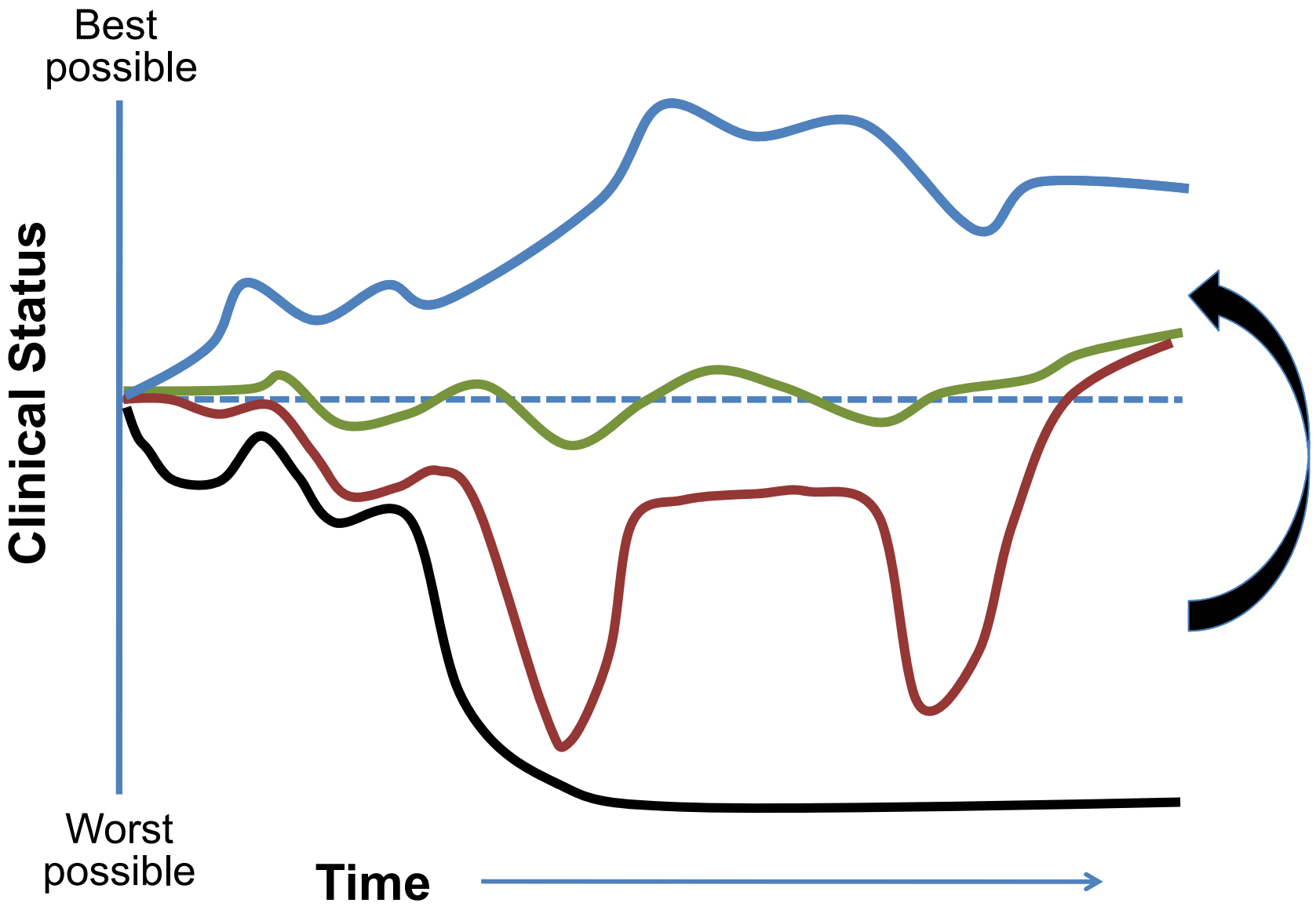
Based on stratified log rank test. For both trials, worst rank is assigned to death (earlier worse than later) and best rank is assigned to patients without worsening event and is based on VAS AUC (better rank in patients with positive AUC than negative AUC).

Primary Endpoint Analyses Based on Ranked and Numerical Approach: Combined Analysis of Pre-RELAX-AHF and RELAX-AHF



Based on stratified log rank test. For both trials, worst rank is assigned to death (earlier worse than later) and best rank is assigned to patients without worsening event and is based on VAS AUC (better rank in patients with positive AUC than negative AUC). Numerical is based on VAS AUC with worst score assignment, adjusted for covariates.

Effect of Serelaxin on Clinical Course



Effect of Serelaxin on the Risk of In-Hospital Worsening Heart Failure

- Is the effect of serelaxin on in-hospital worsening heart failure ***meaningful***?
- Is the effect of serelaxin on in-hospital worsening heart failure ***robust***?
- Is the effect of serelaxin on in-hospital worsening heart failure ***distinctive***?

Current Status of Drugs for Acute Heart Failure

Drug	Current Status of Use in Acutely Decompensated Heart Failure
Diuretics	Furosemide approved for acute pulmonary edema; dose not well defined; insufficient in many patients.
Nitroglycerin	Not approved for acutely decompensated heart failure; efficacy of currently used doses are unknown; frequent development of tolerance; one controlled trial failed to demonstrate efficacy.
Nesiritide	Approved for acutely decompensated heart failure, but evidence for efficacy is weak; neutral effect on long-term mortality
Dopamine	Approved based on short-term hemodynamic effects; no controlled trials demonstrating clinical benefits; concerns that use may cause cardiac injury and arrhythmias and increase risk of death
Dobutamine	
Milrinone	

Analyses Indicate Low Likelihood That Serelaxin Increases All-Cause Mortality

	Hazard ratio (95% CI)
RELAX-AHF (30 µg/kg/day)	0.63 (0.43-0.93)
RELAX-AHF (worst case scenario)	0.74 (0.51-1.07)

Worst case scenario assumes that all patients with missing vital status at 180 days are alive in the placebo group (n=7) but dead in the serelaxin group (n=7) – with no patients being censored

Indication for Use Should Reflect Component Driving the Effect on Primary Endpoint

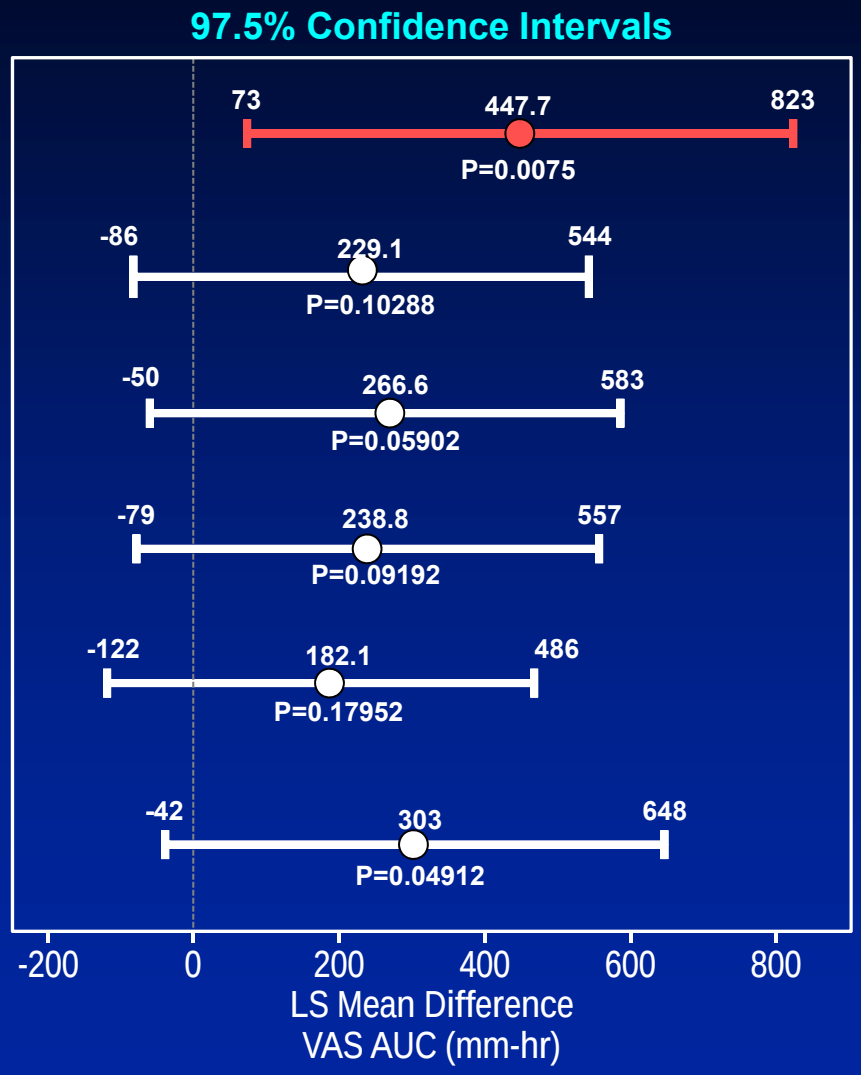
Back-up Slides

REASANZ™ (Serelaxin)
BLA 125,468

March 27, 2014

FDA Requested VAS AUC Sensitivity Analyses

- Primary analysis- Assigned worst reported score after WHF onset (pre-specified analysis)
- FDA 1 – Reported values for WHF with increased IV diuretics or addition of IV nitrates
- FDA 2 – min. of 50%ile worst reported score or the patients reported score for WHF with increased IV diuretics or addition of IV nitrates
- FDA 3 – Reported values after end of WHF
- FDA 4 - Reported values for WHF with increased IV diuretics or addition of IV nitrates after end of WHF
- FDA 5 – Reported values after end of WHF with increased IV diuretics



Rule of assigning the worst reported score after death was retained in all sensitivity analyses.

Primary Endpoint Analyses Based on Clinically Ranked Outcomes Without Use of Arbitrary Numerical Score Assignment

	P value
Analysis of clinically ranked outcomes	
All worsening heart failure events assigned same rank	0.0190
Earlier worsening heart failure events assigned worse rank than later events*	0.0110
Recurrent worsening events assigned worse rank than single events	0.0150
Aggressive interventions ranked worse than IV vasodilators, ranked worse than IV diuretics	0.0183
Prespecified primary efficacy analysis	**0.0075**

*** In Novartis Briefing Book, other sensitivity analysis presented in addendum**

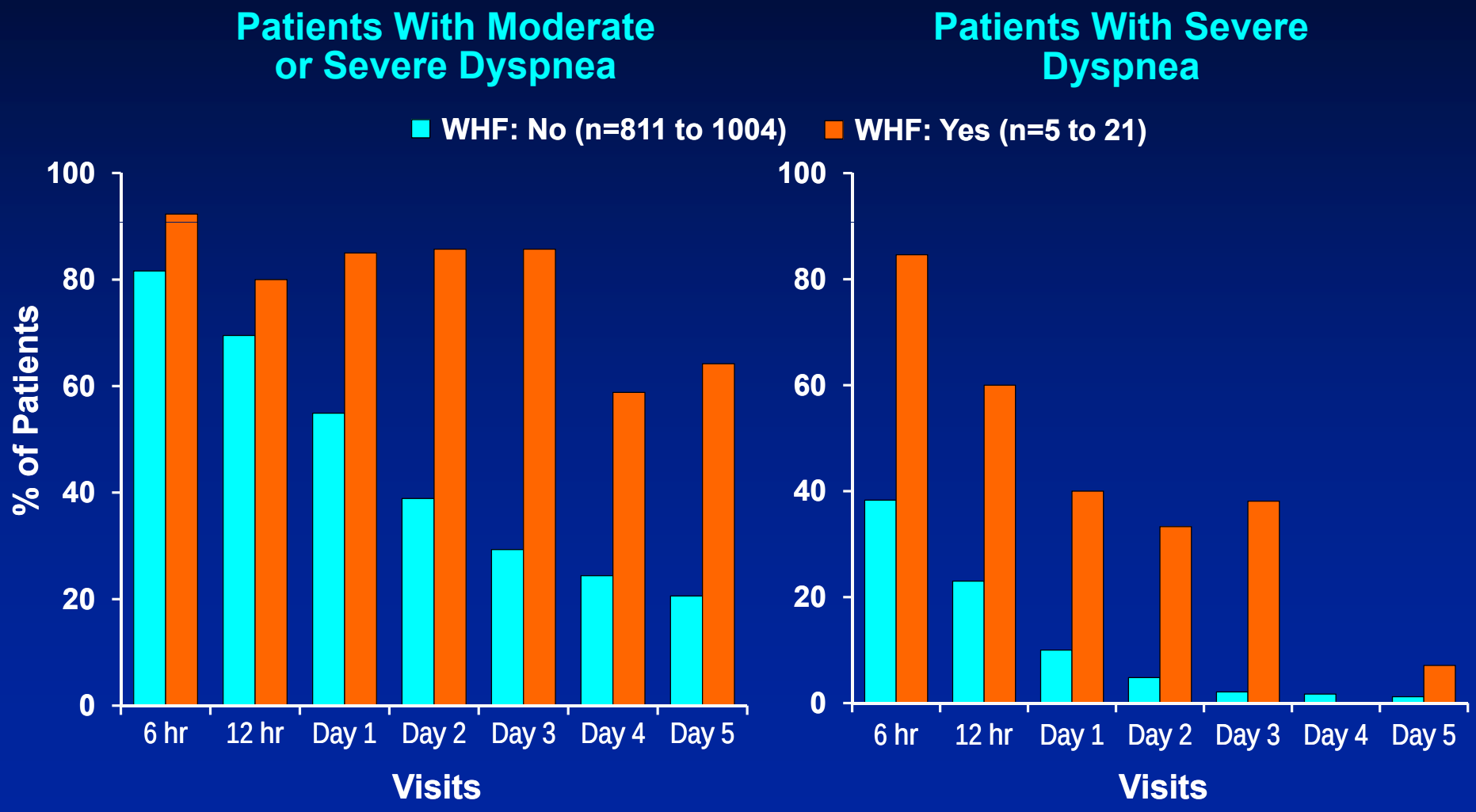
Observed VAS scores and log rank test used
Follows ideas of Finkelstein & Schoenfeld (1999) and Felker (2010)

Corresponding Adverse Events for Patients Experiencing WHF Through Day 5

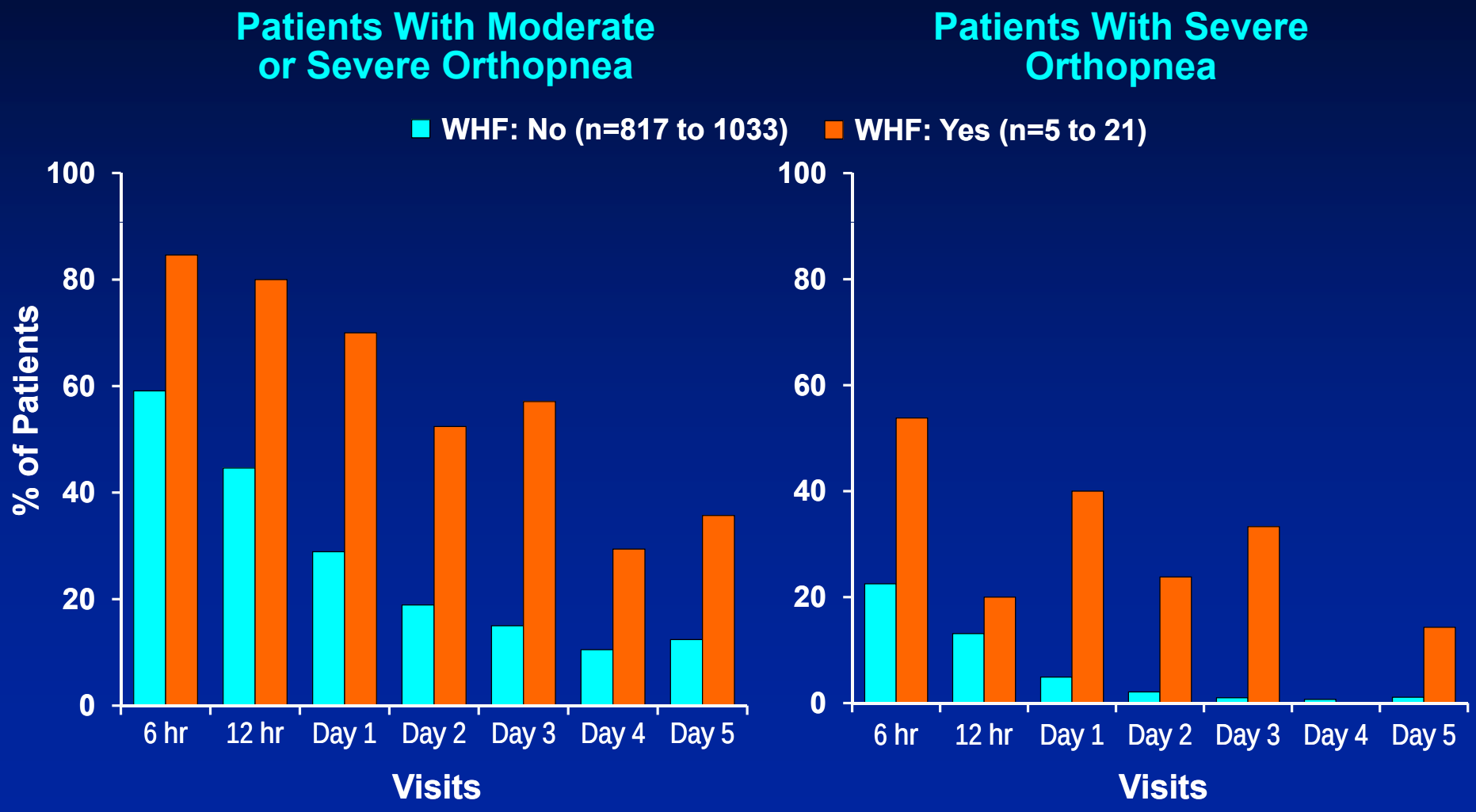
Total number of patients with WHF *		**102**
Total number of patients with AEs identified as related to the WHF event *		**98**
System Organ Class	**Preferred Term**	**n**
Cardiac disorders	**Acute left ventricular failure**	**1**
	Cardiac failure	**11**
	Cardiac failure acute	**5**
	Cardiac failure congestive	**49**
	Cardiogenic shock	**1**
Respiratory, thoracic and mediastinal disorders	**Acute pulmonary edema**	**6**
	Acute respiratory failure	**1**
	Dyspnea	**23**
	Pulmonary congestion	**1**
	Pulmonary edema	**1**
	Respiratory distress	**1**
	Respiratory failure	**1**
General disorders	**Edema peripheral**	**1**

*** Patients died or rehospitalized for HF through Day 5 without prior WHF events were excluded; patients could have more than one WHF-related AEs**

Physician-Assessed Dyspnea in WHF Patients at Visit After Event Onset: Comparison With Non-WHF Patients



Orthopnea in WHF Patients at Visit After Event Onset: Comparison With Non-WHF Patients



RELAX-AHF – Safety Population

Summary of Confirmed Blood Pressure Decrease Event (CBPDE) subgroups by Baseline Systolic BP <130 mmHg and above

Treatment Group	BL SBP Category	n (%)	CBPDE; n (%)			
			Any CBPDE N=167	Dose Decrease only N=59	Dose Discontinuation N=91	Dose Decrease Followed by Discont. N=16
Placebo (N=570)	< 130	118	30 (25.4)	1 (0.8)	29 (24.6)	0
	130 - < 140	161	19 (11.8)	1 (0.6)	18 (11.2)	0
	140 - < 152	152	20 (13.2)	3 (2.0)	8 (5.3)	9 (5.9)
	≥ 152	138	33 (23.9)	26 (18.8)	4 (2.9)	3 (2.2)
Serelaxin (N=568)	< 130	101	42 (41.6)	2 (2.0)	39 (38.6)	1 (1.0)
	130 - < 140	188	40 (21.3)	1 (0.5)	36 (19.1)	3 (1.6)
	140 - < 152	138	34 (24.6)	14 (10.1)	14 (10.1)	6 (4.3)
	≥ 152	140	50 (35.7)	42 (30.0)	2 (1.4)	6 (4.3)

Source: AC Table 14.3-24.1

Outcomes of Patients With/Without Confirmed Blood Pressure Decrease Event (CBPDE)

Parameter	Placebo (N=570)		Serelaxin (N=568)	
	Without CBPDE	With CBPDE	Without CBPDE	With CBPDE
Patient number; n (%)	467 (81.9)	103 (18.1)	401 (70.6)	167 (29.4)
Duration of infusion in hours; mean (SD)	47.0 (5.7)	29.4 (16.1)	46.8 (5.8)	27.9 (18.5)
VAS AUC of change from baseline to Day 5 (mm-hr); mean	2478	1632	2850	2657
WHF to Day 5; n (%)	50 (10.8)	19 (18.6)	25 (6.3)	12 (7.2)
CV death or HF/RF re-hospitalization to Day 60; n (%)	61 (13.1)	14 (13.6)	48 (12.0)	26 (15.6)
All-cause mortality through Day 180; n (%)	51 (10.9)	13 (12.6)	28 (7.0)	13 (7.9)

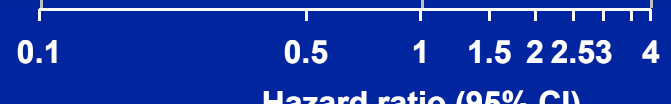
Subgroup Analyses of VAS AUC and All-Cause Mortality by Baseline SBP

VAS AUC Through Day 5

	Placebo VAS AUC Mean	Serelaxin VAS AUC Mean	LS Mean (mm-hr) Difference (95%CI)	P value
≥152 mmHg	2239.2	2907.8	668.6 (3.5, 1333.8)	
140-<152 mmHg	2553.2	2924.4	371.2 (-284.5, 1026.8)	0.9143
130-<140 mmHg	2359.5	2797.0	437.5 (-159.1, 1034.0)	
<130 mmHg	2003.5	2366.5	363.0 (-376.7, 1102.7)	
All patients	2307.9	2755.6	447.7 (120.0, 775.4)	

180-day All-Cause Mortality

	Placebo K-M Est (%)	Serelaxin K-M Est (%)	Hazard Ratio Estimate (95%CI)	P value
≥152 mmHg	5.7	4.3	0.75 (0.26, 2.16)	
140-<152 mmHg	12.4	6.5	0.52 (0.23, 1.41)	0.5499
130-<140 mmHg	11.1	5.2	0.46 (0.21, 1.00)	
<130 mmHg	16.4	15.0	0.89 (0.46, 1.72)	
All patients	11.2	7.2	0.63 (0.43, 0.93)	

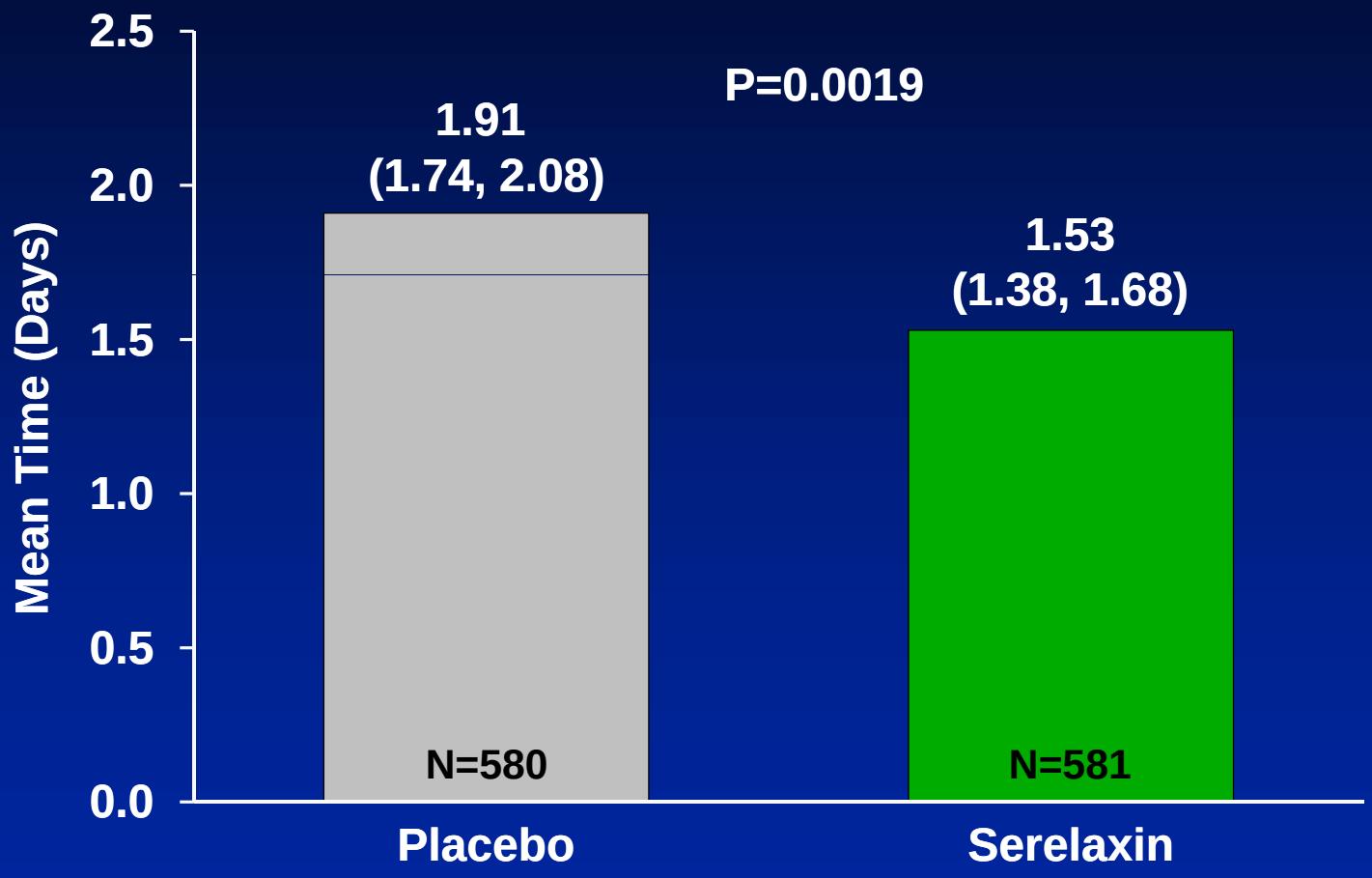


Excerpt from RELAX-AHF Study Protocol

9.8.1 Area under the change from baseline dyspnea VAS curve from baseline to Day 5

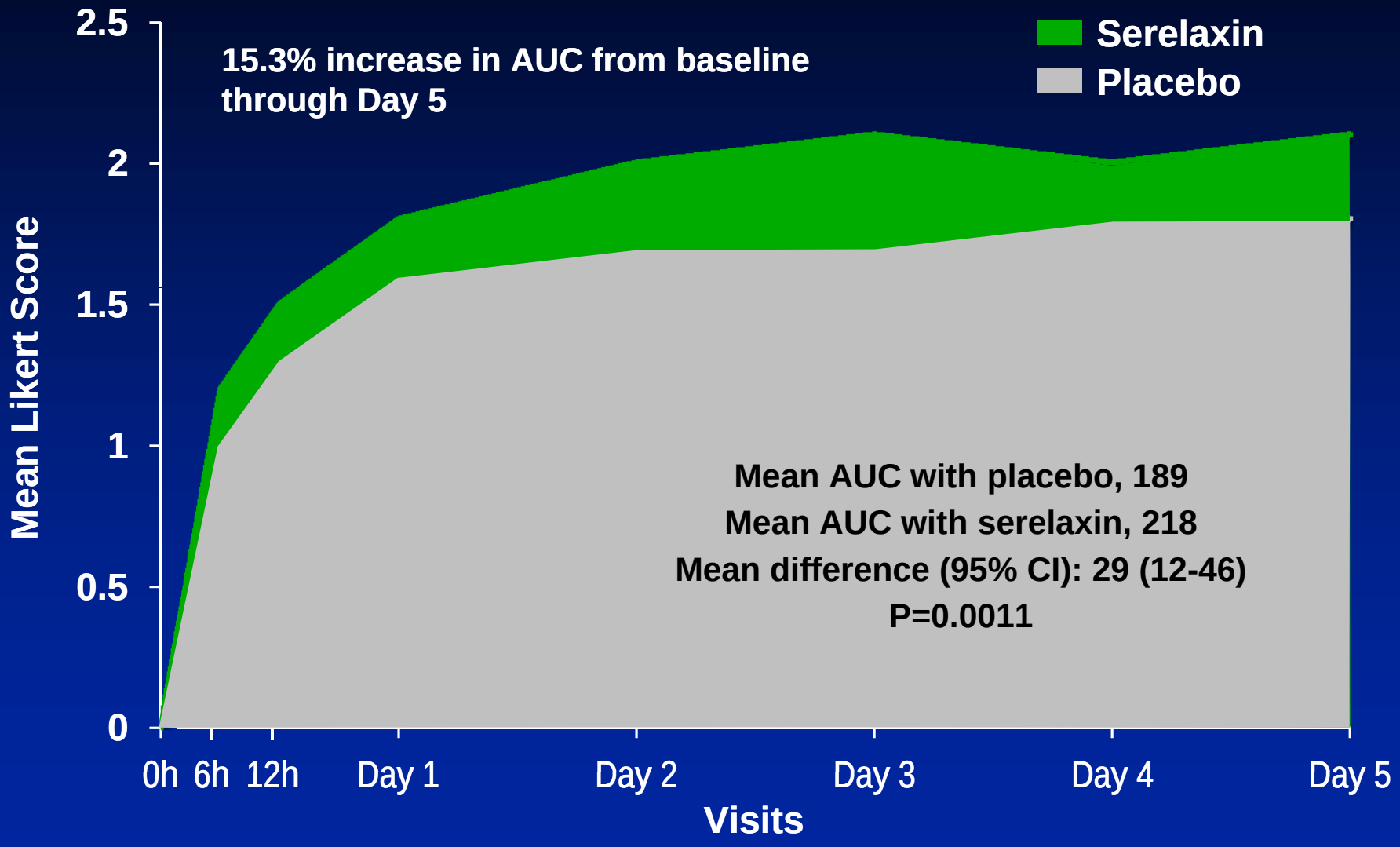
The area under the curve representing the change from baseline in dyspnea VAS score from baseline through Day 5 (VAS AUC) will be computed by trapezoidal rule after applying the following data handling conventions. For subjects who die or have a worsening heart failure event (either during the index hospitalization or rehospitalization for heart failure) by Day 5, the worst score observed in any subject at any time point will be carried forward for all time points after the time of onset of the event, regardless of whether the score is missing or not. For post-baseline values otherwise missing, a missing score will be imputed using linear interpolation between the last preceding and first following non-missing values; if no following non-missing value is available, the last available preceding value will be carried forward. A missing baseline score will be imputed as the earliest, non-missing score within 24 hours for the subject minus the average change from baseline in the study population to that time point; post-baseline scores for subjects for whom a missing baseline cannot be thus imputed will be included in the analysis as no change from baseline. Except for subjects who die or who experience worsening heart failure, subjects who are missing all post-baseline dyspnea VAS scores will be included in the analysis as having no change from baseline at any time point. Treatment groups will be compared using a t-test as the primary method. If results suggest noteworthy departures from the assumptions underlying the t-test, supportive analyses such as the Wilcoxon rank sum test or a randomization-based determination of the p-value for the t-test may be conducted.

Time to Moderate or Markedly Improvement by Likert Scale to Day 5



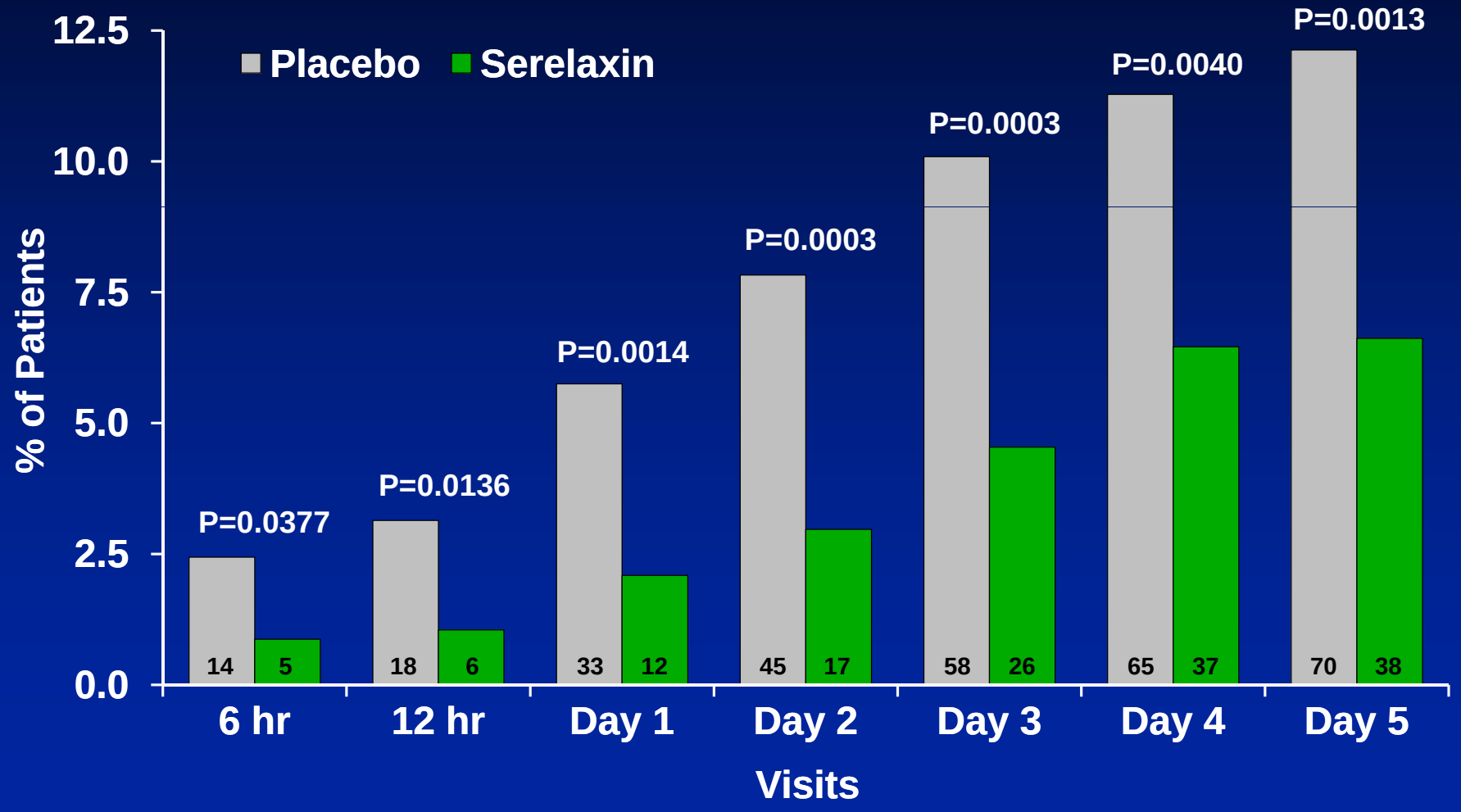
P value based on a Wilcoxon rank test
Data presented as mean ± 95% CI

Dyspnea Assessment by Likert: AUC Day 0-5



P value based on a two-sided two sample t-test

Dyspnea Assessment by Likert: Mean % of Moderately or Markedly Worsening Dyspnea Through Day 5



P values based on Wilcoxon test

AEs Through Day 5 of Renal Impairment and Failure for Patients With Baseline SBP <130 mmHg

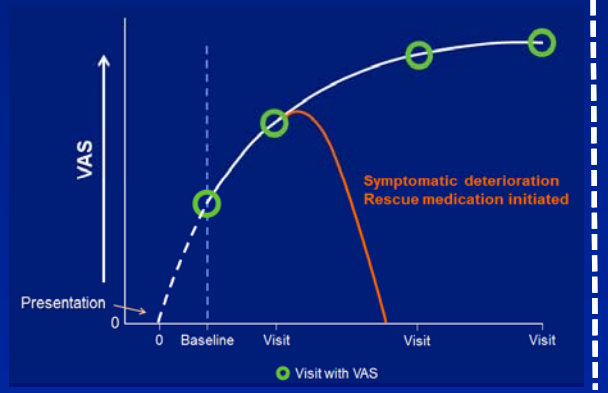
	Pooled	
	Placebo (N=129)	Serelaxin 30 µg/kg/day (N=108)
Renal and Urinary disorder SOC	6 (4.7)	7 (6.5)
Azotaemia	0	1 (0.9)
Dysuria	0	0
Haematuria	1 (0.8)	2 (1.9)
Leukocyturia	0	0
Oliguria	0	0
Proteinuria	0	0
Renal artery stenosis	0	0
Renal colic	0	0
Renal failure acute	0	0
Renal failure	4 (3.1)	3 (2.8)
Renal impairment	1 (0.8)	0
Urethral haemorrhage	0	0
Urinary retention	0	0
Urinary tract disorder	0	1 (0.9)

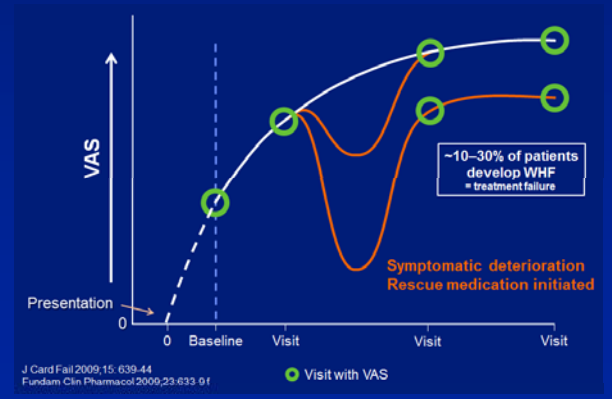
Visual Analog Scale Area Under the Curve Was Designed as a Composite Endpoint

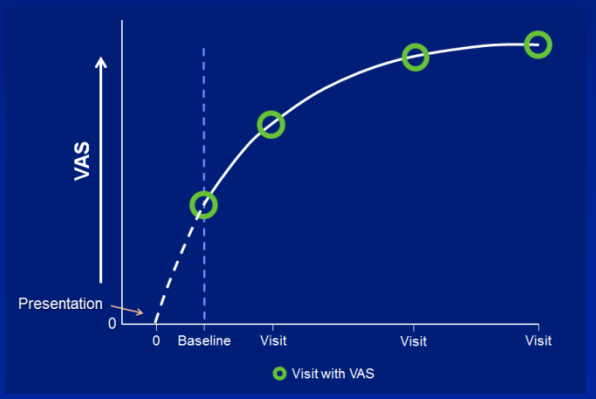
Death

In-hospital worsening heart failure

Change in dyspnea score







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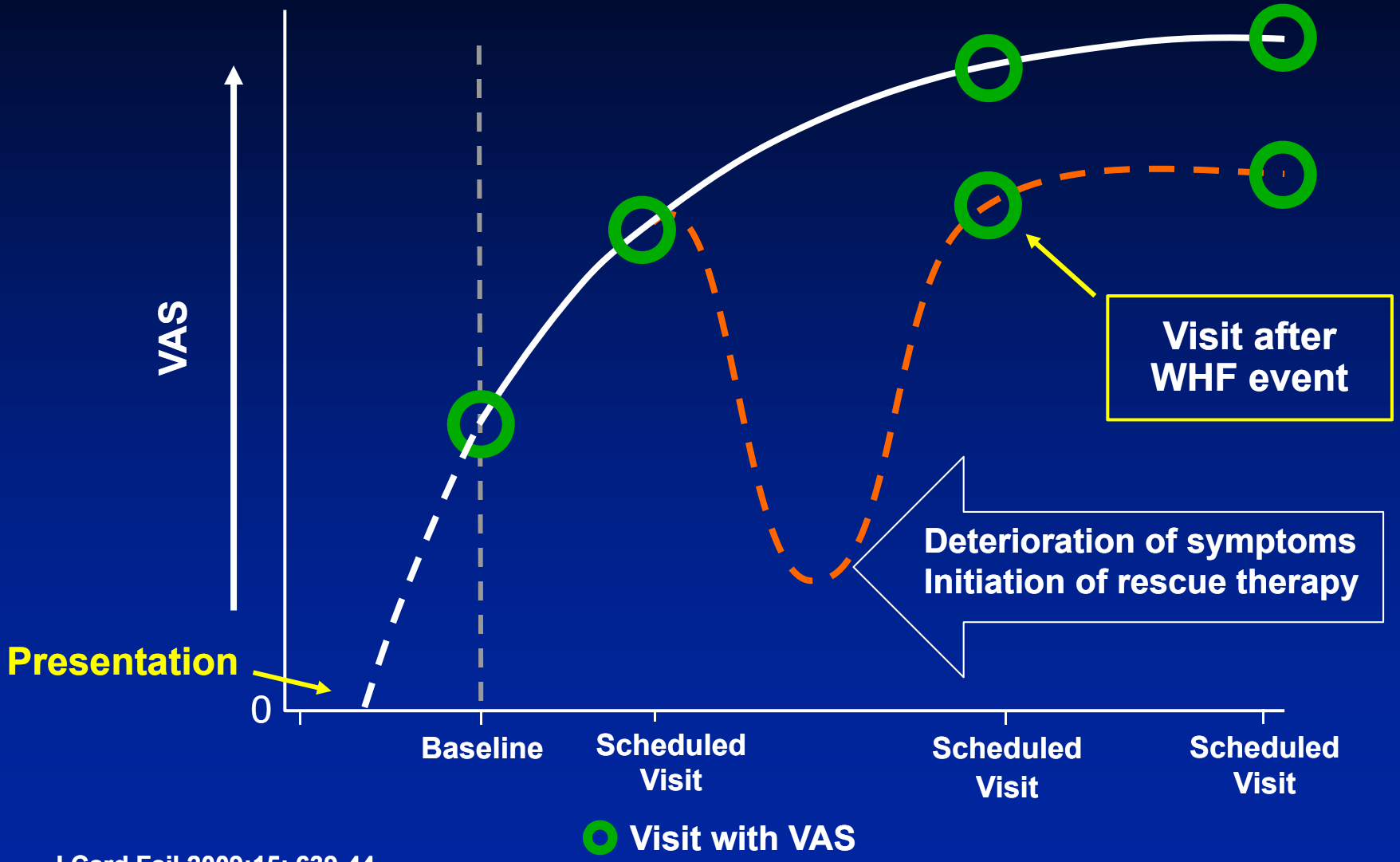
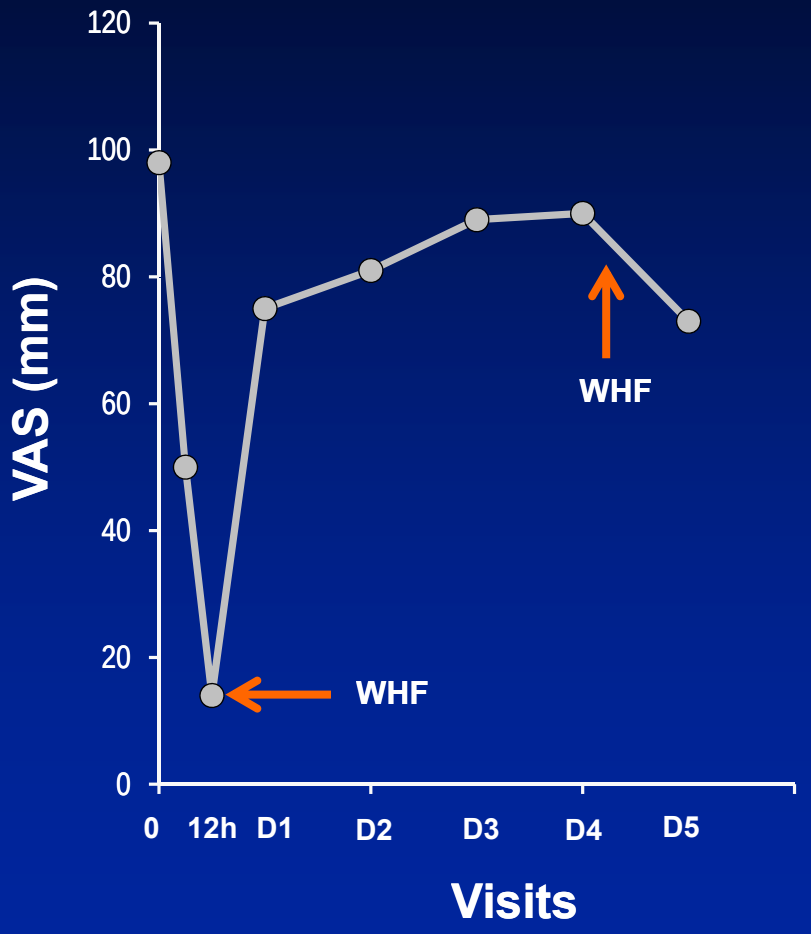
Schematic of a Patient's Clinical Course With Dyspnea and a WHF Event



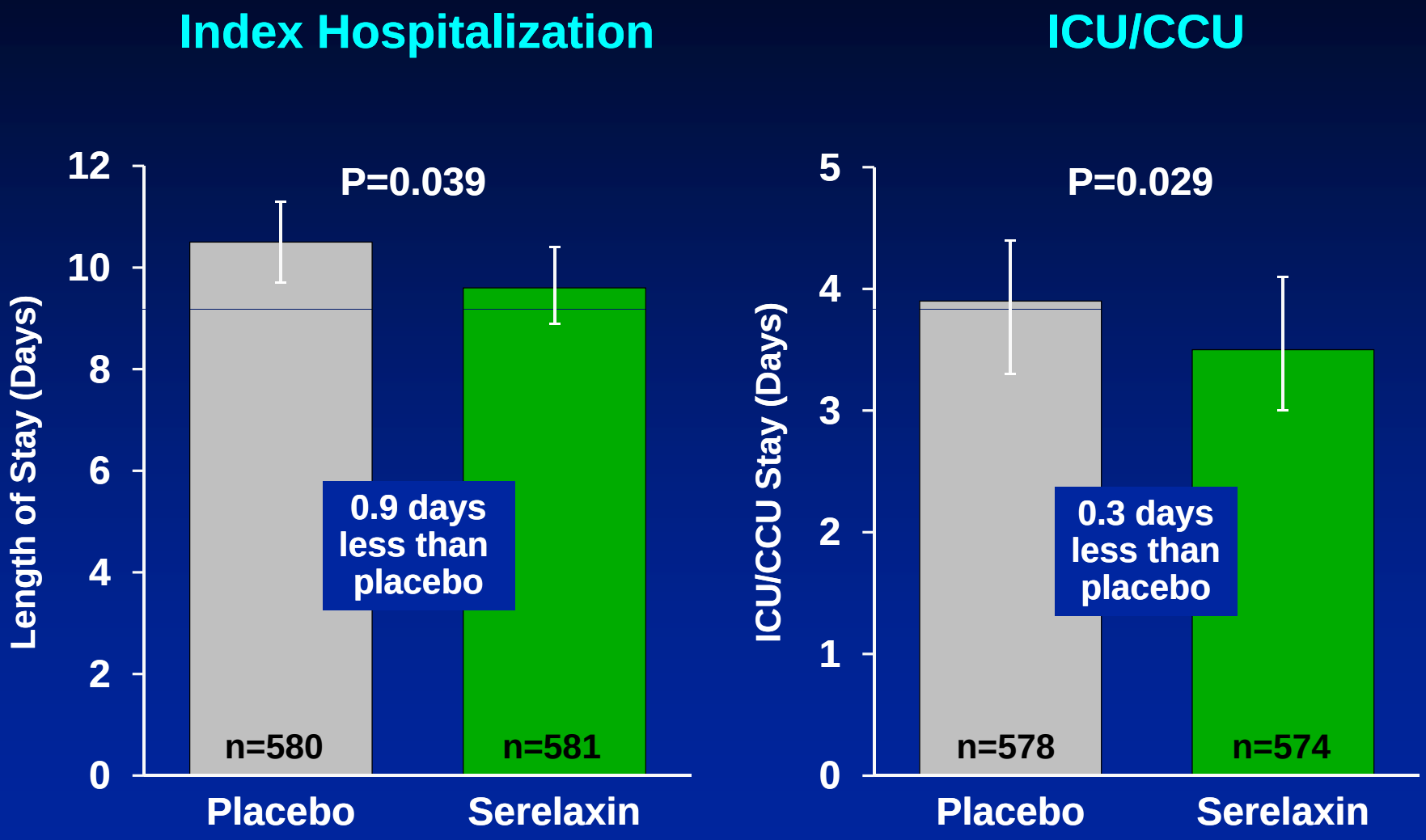
J Card Fail 2009;15: 639-44
Fundam Clin Pharmacol 2009;23:633-9

Clinical Course of WHF Patient (#7710-003) Highlighted in FDA Briefing Document

- **75 y/o man entered the study with prior history of CHF (NYHA III), MI, hypertension, PVD, chronic AFib, and T2DM**
  - Presented with dyspnea. NT-proBNP >3,000 pg/mL, baseline BP 155/81
  - Received 80 mg IV furosemide prior to initiation of study drug infusion
  - Developed WHF event on Day 1 requiring intensification of IV diuretic (120 mg furosemide) and initiation of IV nitroglycerin; AE of dyspnea with moderate severity reported
  - Recurrent WHF event on Day 4, and received IV furosemide and nitroglycerin; AE of pulmonary edema with moderate severity reported
  - Discharge on Day 14
  - Rehospitalized for HF on Day 16



Length of Stay in Hospital and ICU/CCU



P value by Wilcoxon rank sum test (death assigned longest length of stay plus 1 day)

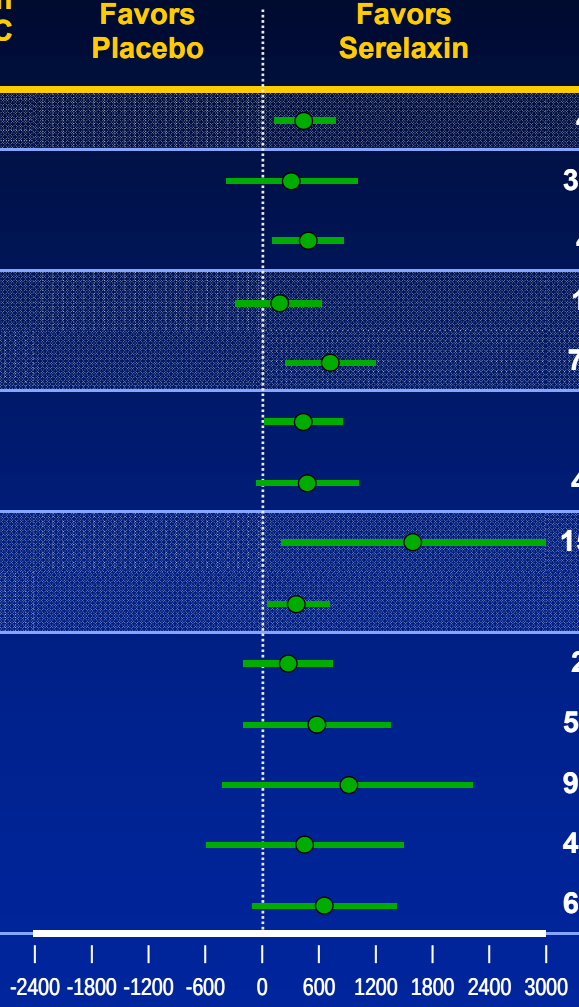
Baseline Patient Characteristics of RELAX-AHF Compared to US AHF Registries

	ADHERE[1] (N=107,920)	OPTIMIZE[2] (N=34,059)	RELAX-AHF (N=1,161)
Mean age (years)	75.3	73.6	72.0
Women (%)	52	52	38
SBP (mmHg)	144	143	142
Prior CHF (%)	75	87	74
LVEF <40% (%)	59	52	55
eGFR <60 ml/min/1.73m^2 (%)	64	N/A	70
Ischemic heart disease (%)	57	50	52
Hypertension (%)	72	71	87
Atrial fibrillation-hx (%)	31	31	52
Diabetes (%)	44	42	48

1. Gheorghiade et al. Am J Cardiol 2005; 96(suppl):11G–17G
2. Heywood et al. J Cardiac Fail 2007;13:422–30

Dyspnea Assessment by VAS – Subgroup Analysis

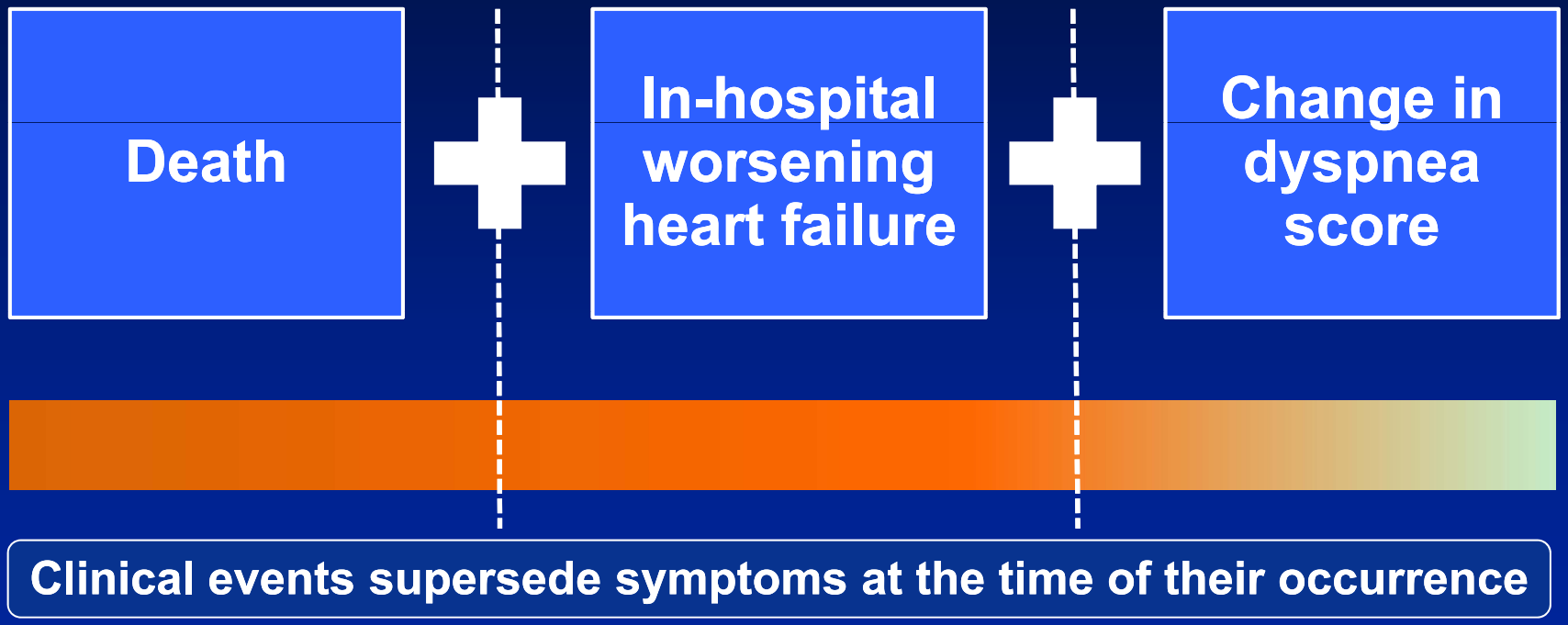
Subgroup		Placebo VAS AUC Mean	Serelaxin VAS AUC Mean	LS Mean (mm-hr) Difference (95%CI	Interaction P value
Overall		2307.9	2755.6	447.7 (120.0, 775.4)	
Age (<65 ≥65)	<65	2325.0	2634.7	309.7 (-381.4, 1000.8)	0.6484
	≥65	2303.5	2795.8	492.3 (119.1, 865.6)	
Age (<75 ≥75)	<75	2483.5	2675.7	192.2 (-259.6, 644.0)	0.1113
	≥75	2124.9	2850.3	725.4 (249.1, 1201.6)	
Gender	Male	2193.7	2634.5	440.8 (26.3, 855.3)	0.9230
	Female	2490.7	2964.9	474.1 (-60.5, 1008.7)	
Race	Other Race	1967.0	3563.2	1596.2 (198.6, 2993.7)	0.0960
	White/Caucasian	2325.2	2700.7	375.5 (38.4, 712.5)	
Region	Eastern EU	2235.9	2509.0	273.1 (-196.5, 742.7)	0.8498
	Western EU	1924.0	2502.5	578.6 (-200.9, 1358.1)	
	South America	2771.1	3674.6	903.5 (-418.9, 2225.9)	
	North America	2428.3	2877.6	449.3 (-594.0, 1492.6)	
	Israel	2644.3	3295.4	651.1 (-117.2, 1419.3)	



Mean treatment difference and P value for interaction are from ANCOVA model with treatment, subgroup, and treatment*subgroup interaction as covariates.

Interaction P values are based on a Cox model with treatment, subgroup and treatment-subgroup interaction.

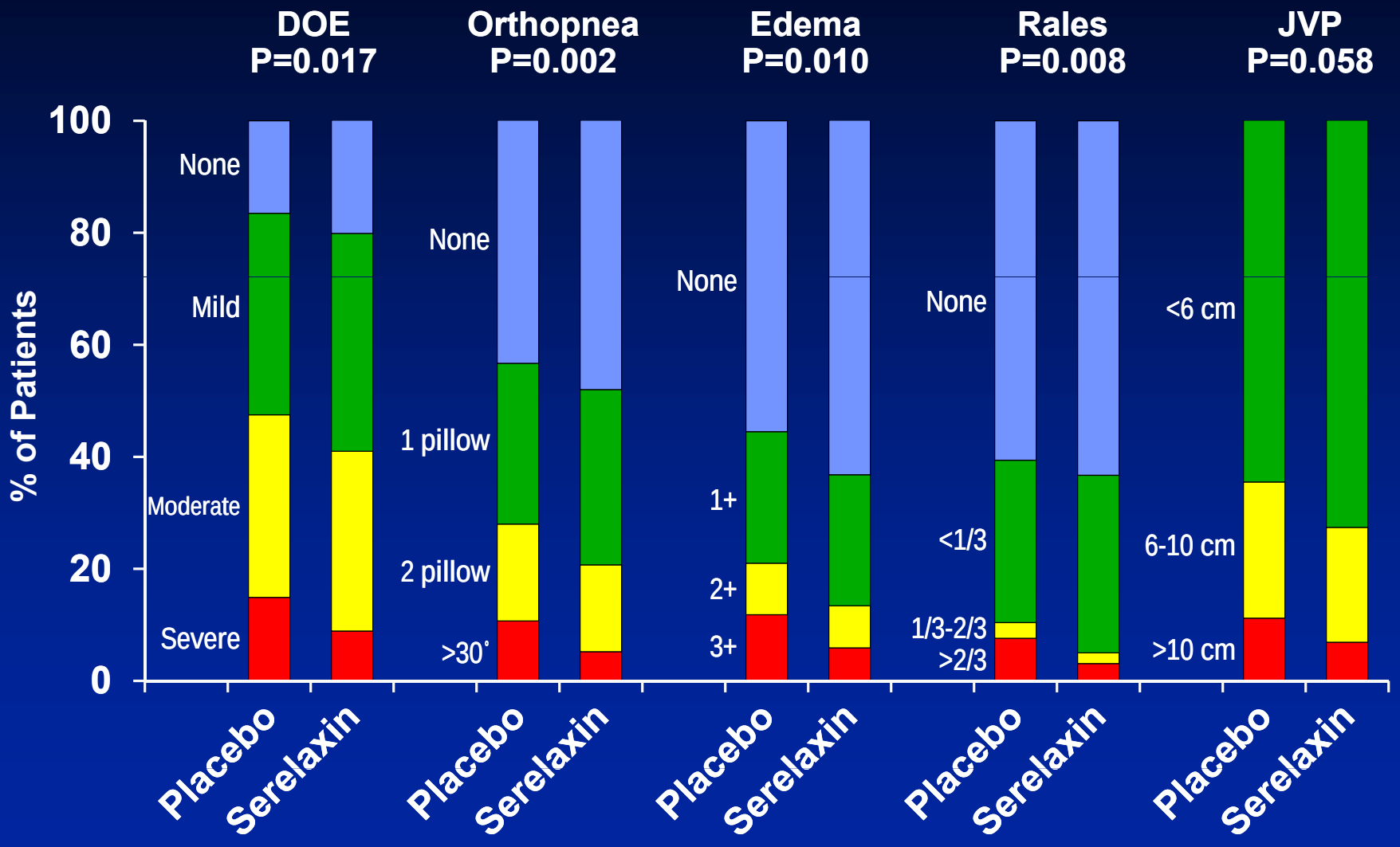
Visual Analog Scale Area Under the Curve Was Designed as a Composite Endpoint



In-Hospital Worsening Heart Failure Has Been Analyzed as Treatment Failure in Contemporary AHF Trials

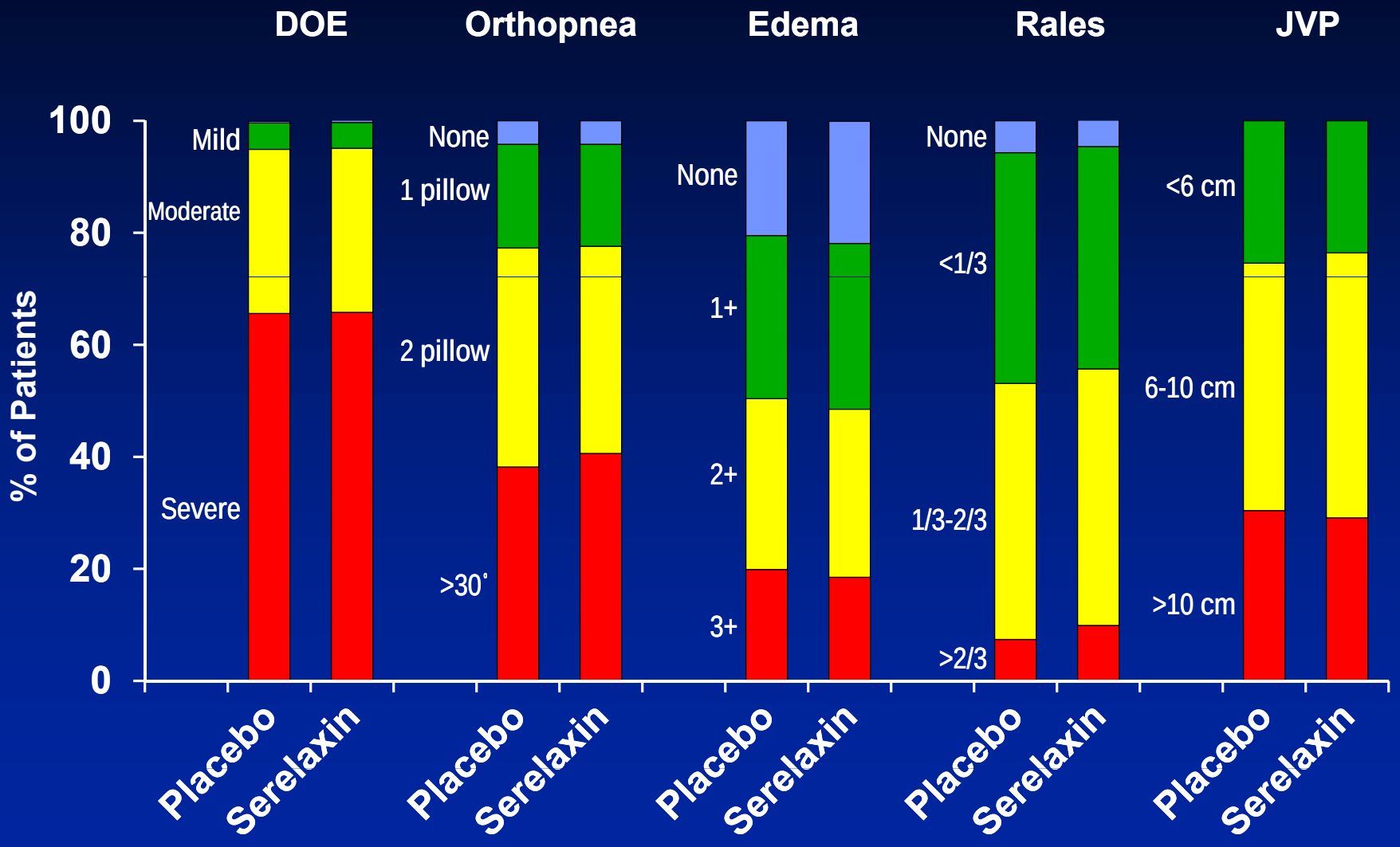
Trial	Drug	In-Hospital WHF Incorporated into Primary Endpoint
EVEREST	Tolvaptan	No
ASCEND	Nesiritide	No
VERITAS	Tezosentan	Worst rank or score
REVIVE	Levosimendan	Worst rank or score
PROTECT	Rolofylline	Worst rank or score
RELAX-AHF	Serelaxin	Worst rank or score
TRUE-AHF	Ularitide	Worst rank or score

Signs and Symptoms of Heart Failure at Day 2 by Treatment



P values based on 2-sided Wilcoxon rank sum test (WHF assigned worst score)

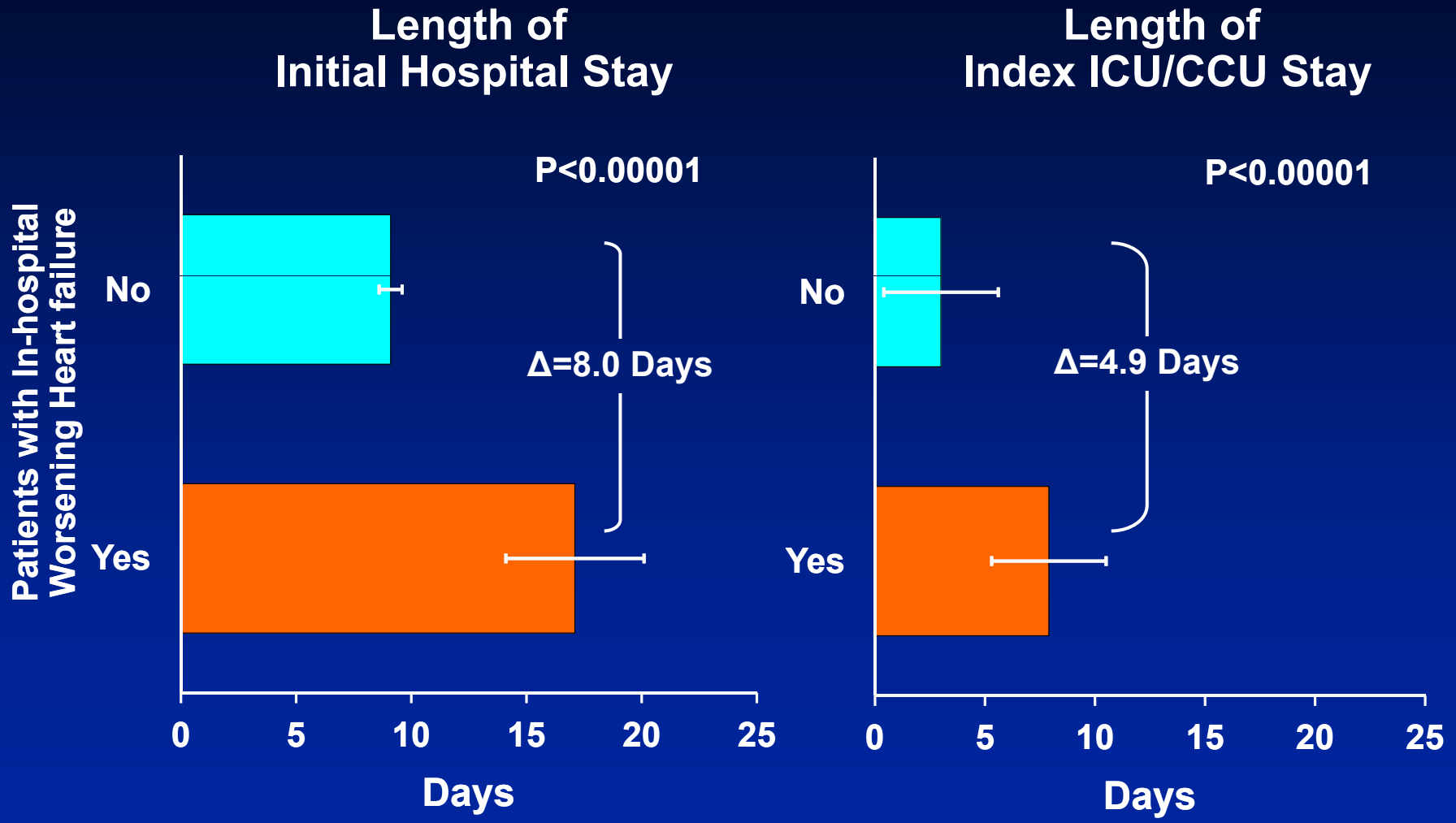
Signs and Symptoms of Heart Failure at Baseline by Treatment



Baseline Medical History of Patients in RELAX-AHF

	Placebo (N=580)	Serelaxin (N=581)
Medical History, n (%)		
Hypertension	510 (87.9)	496 (85.4)
Hyperlipidemia	313 (54.0)	304 (52.3)
Ischemic Heart Disease	307 (52.9)	296 (50.9)
Atrial fibrillation - hx	305 (52.6)	297 (51.1)
Atrial fibrillation at screening	246 (42.5)	233 (40.2)
Diabetes Mellitus	272 (46.9)	279 (48.0)
Stroke or Other Cerebrovascular Event	84 (14.5)	73 (12.6)
Cigarette Smoking	81 (14.0)	72 (12.4)
Peripheral Vascular Disease	82 (14.1)	73 (12.6)
Mitral Regurgitation	182 (31.4)	179 (30.8)
Pacemaker	58 (10.0)	63 (10.8)
Biventricular Pacing	52 (9.0)	61 (10.5)
Implantable Cardiac Defibrillator	75 (12.9)	79 (13.6)
Asthma, Bronchitis, or COPD	88 (15.2)	96 (16.5)

Patients With Worsening Heart Failure Had Prolonged Intensive Care and Hospital Stay



Patients with worsening heart failure (n=99) and without worsening heart failure (n=1055)
Excludes patients who died through Day 5. Data are presented as mean ±95% CI

Association of WHF to Day 5 with Death Through Day 180

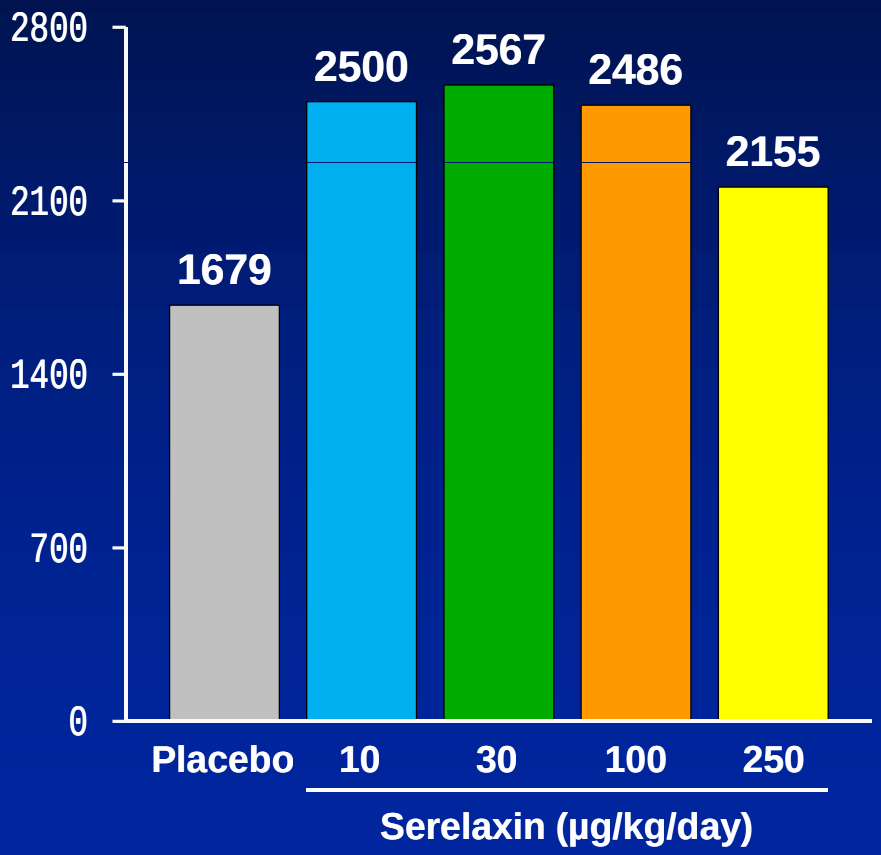
Death through Day 180	Hazard Ratio (95% CI), Unadjusted [1]	P value	Hazard Ratio (95% CI), Adjusted [2]	P value
PROTECT Pilot	2.06 (0.92, 4.64)	0.0808	–	–
PROTECT	2.78 (2.16, 3.57)	<.0001	–	–
Pre-RELAX-AHF	4.15 (1.61, 10.72)	0.0032	–	–
RELAX-AHF	1.91 (1.08, 3.37)	0.0252	–	–
Combined	2.61 (2.20, 3.10)	<.0001	1.93 (1.55, 2.41)	<.0001

[1] Effect of WHF from univariable models
[2] Adjusted for covariates in the multivariable model for the outcome

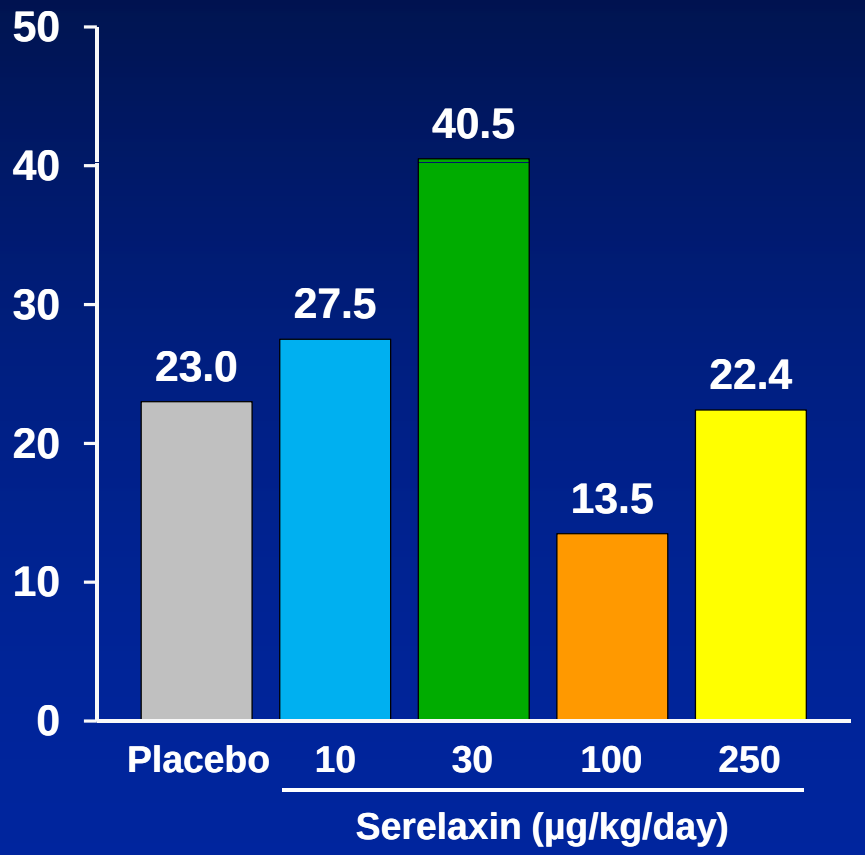
Note: Patients who died by 5 days were excluded from all models. Patients with a censored time by 5 days were excluded from time-to-event models..
B Davison et al with collaboration with Merck and company

Pre-RELAX-AHF: VAS AUC and Likert Responders

Visual Analog Scale AUC Through Day 5 (mm-hr)



Proportion With Moderate/Marked Improvement on Likert Scale at 6h, 12h and 24h



Teerlink et al., Lancet 2009; 373: 1429-39

Dose Selection in Pre-RELAX-AHF

		Placebo (N=61)	10 µg/kg/d (N=40)	30 µg/kg/d (N=42)	100 µg/kg/d (N=37)	250 µg/kg/d (N=49)
Symptoms	1. Mean VAS AUC change from baseline to Day 5 (mm-hr)	1,679	2,500	2,567	2,486	2,155
	2. Proportion of patients with moderate/marked improvement by Likert at 6, 12 and 24 hrs (%)	23.0	27.5	40.5	13.5	22.4
Short-Term Outcomes	3. WHF to Day 5 (%)	21.3	20.0	11.9	13.5	10.2
	4. Mean length of hospital stay (days)	12.0	10.9	10.2	11.1	10.6
	5. Persistent renal impairment (Creatinine ↑ ≥0.3 mg/dL at Day 5 and 14) (%)	6.8	7.5	7.3	10.8	15.2
Longer-Term Outcomes	6. Mean days alive and out of hospital through Day 60 (days)	44.2	47.0	47.9	48.0	47.6
	7. Proportion of patients with CV death or rehospitalization due to HF or renal failure through Day 60 (%)	17.2	10.1	2.6	8.4	6.2
	8. K-M estimate CV mortality to Day 180(%)	14.3	2.5	0.0	2.9	6.2

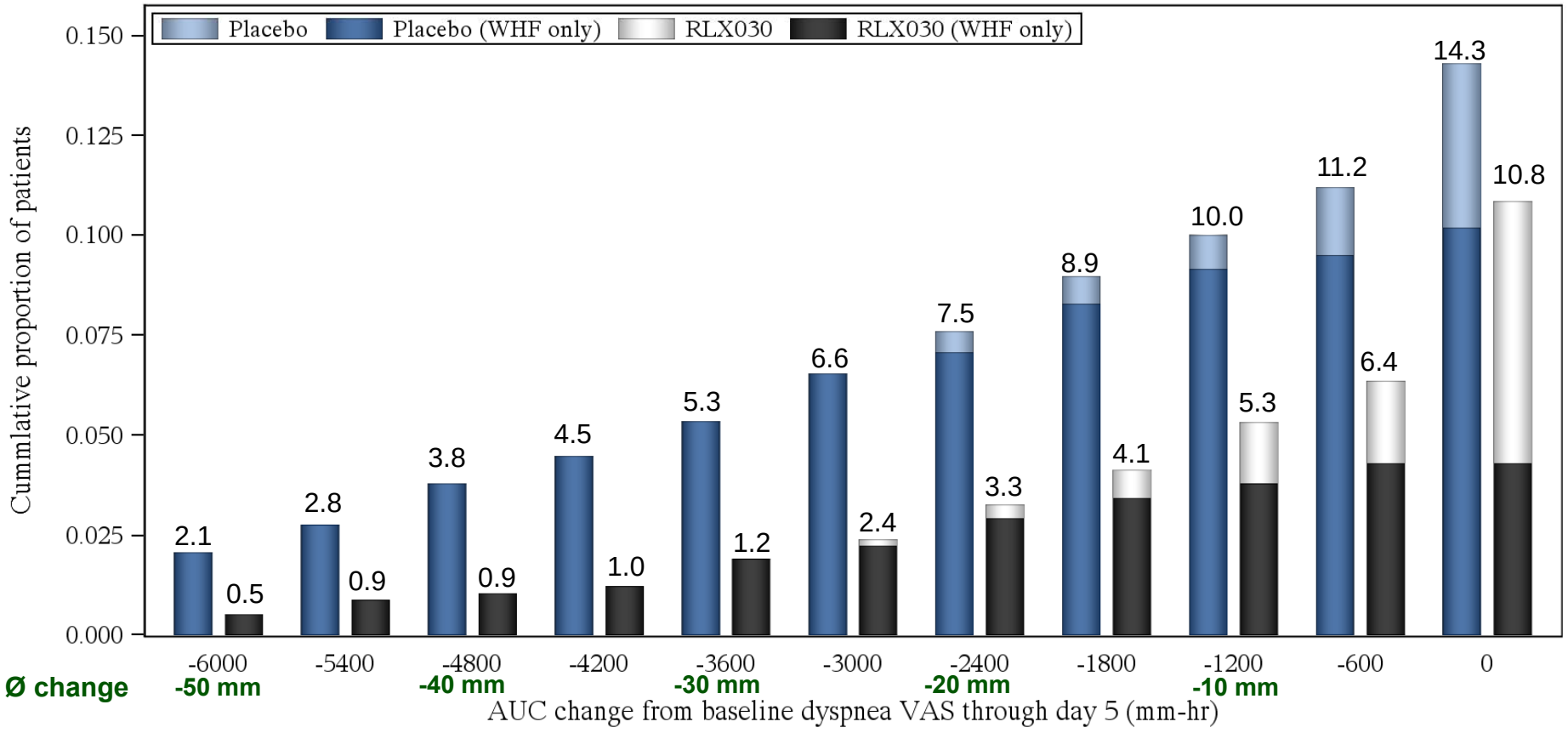
P<0.05 | 0.05 ≤ P<0.20 | P<0.20 against

180-day All-Cause Mortality in Patients With or Without WHF Through Day 5: RELAX and Pre-RELAX-AHF

	Pooled Pre-RELAX-AHF and RELAX-AHF (30 µcg/kg/day)		RELAX-AHF	
	Placebo (N=642)	Serelaxin (N=753)	Placebo (N=580)	Serelaxin (N=581)
WHF: No				
n	560	582	511	544
Number of Events (K-M estimate)	55 (10.1)	35 (6.2)	52 (10.3)	33 (6.2)
WHF: Yes				
n	78	39	65	34
Number of Events (K-M estimate)	14 (18.2)	7 (18.3)	9 (13.9)	6 (17.7)
Hazard Ratio (95% CI)	1.90 (1.05, 3.43)	3.22 (1.42, 7.26)	1.41 (0.69, 2.86)	3.13 (1.31, 7.47)
P value	0.0325	0.0050	0.3435	0.0101

Patients who died or rehospitalized prior to Day 5 excluded

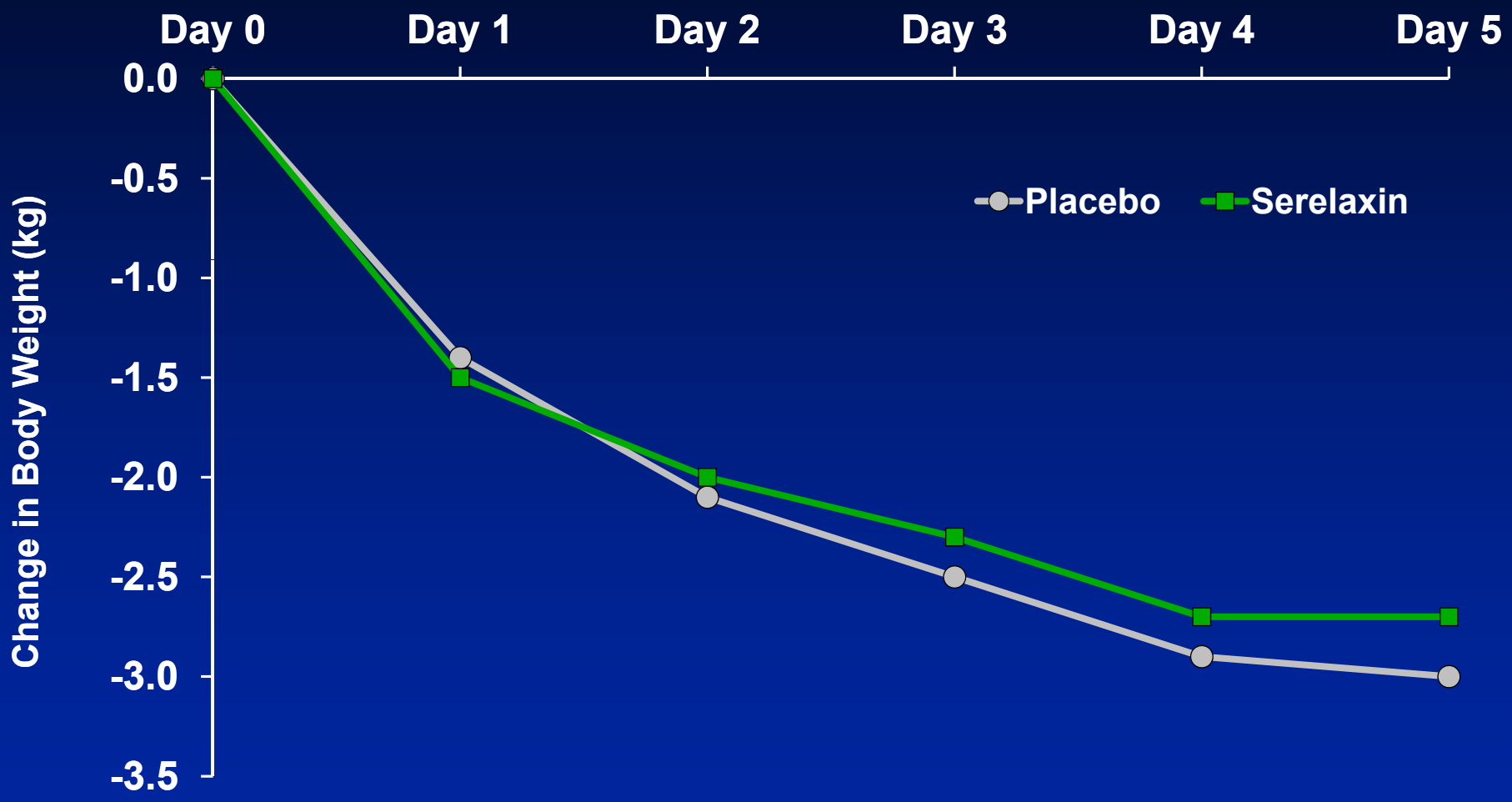
Cumulative Distribution of AUC (mm-hr) of Change of Dyspnea VAS from Baseline to Day 5 by Treatment and WHF (ITT)



The cumulative proportion of patients with a WHF event through Day 5 are displayed within the treatment group bars.

A negative value represents an unfavorable outcome and a positive value represents a favorable outcome.

Change in Body Weight by Day (kg)



Cardiovascular Mortality Through Day 180

Serelaxin	581	563	555	546	542	536	463
Placebo	580	559	547	535	523	514	444

The hazard ratio and CI based on a Cox regression model with treatment as a factor
P value by log rank test